

CLINICAL STUDY PROTOCOL
A PROSPECTIVE, RANDOMIZED, OPEN-LABEL,
BLINDED ENDPOINT EVALUATION (PROBE)
PARALLEL GROUP STUDY COMPARING EDOXABAN
VS. VKA IN SUBJECTS UNDERGOING CATHETER
ABLATION OF NON-VALVULAR ATRIAL
FIBRILLATION (ELIMINATE-AF)

DSE-EDO-01-16-EU

EudraCT NUMBER 2016-003069-25

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INVESTIGATOR AGREEMENT

**A PROSPECTIVE, RANDOMIZED, OPEN-LABEL, BLINDED ENDPOINT
EVALUATION (PROBE) PARALLEL GROUP STUDY COMPARING EDOXABAN VS.
VKA IN SUBJECTS UNDERGOING CATHETER ABLATION OF NON-VALVULAR
ATRIAL FIBRILLATION (ELIMINATE-AF)**

Sponsor Approval:

This clinical study protocol has been reviewed and approved by:

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Investigator's Signature:

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representative.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Council on Harmonization guidelines on Good Clinical Practice (ICH E6), and applicable regional regulatory requirements.

I agree to make available to Sponsor personnel, their representatives and relevant regulatory authorities, my subjects' study records in order to verify the data that I have entered into the case report forms. I am aware of my responsibilities as a Principal Investigator as provided by the Sponsor.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

Date

Signature

Site no.

Investigator's name and address (print or stamp)

PROTOCOL SYNOPSIS

EudraCT Number:	2016-003069-25
Protocol Number:	DSE-EDO-01-16-EU
Investigational Product:	Edoxaban (DU-176b)
Active Ingredient(s)/ international non-proprietary name:	N-(5-Chloropyridin-2-yl)-N'-[(1S,2R,4S)-4-(N,N-dimethylcarbamoyl)-2-(5-methyl-4,5,6,7-tetrahydro[1,3]thiazolo[5,4-c]pyridine-2-carboxamido)cyclohexyl]oxamide mono (4-methylbenzenesulfonate) monohydrate/Edoxaban
Study Title:	A Prospective, Randomized, Open-Label, Blinded Endpoint <u>E</u> valuation (PROBE) Parallel Group Study <u>C</u> omparing Edoxaban vs. VKA <u>i</u> n Subjects Undergoing <u>C</u> atheter Ablation of Non-valvular <u>A</u> trial <u>F</u> ibrillation (ELIMINATE-AF)
Study Phase:	Phase 3b
Indication Under Investigation:	Non-valvular atrial fibrillation (AF)
Study Objectives:	<p>Primary objectives of this study:</p> <p>Primary efficacy objective:</p> <p>To compare <u>descriptively</u> the incidence of the composite of all-cause death, stroke (ischemic, hemorrhagic, or undetermined) and Major Bleeding (International Society on Thrombosis and Hemostasis [ISTH] definition) in the edoxaban group against the vitamin K antagonist (VKA) group in subjects undergoing catheter ablation of atrial fibrillation (AF) in the period from the end of the catheter ablation procedure to Day 90/end-of-treatment (EOT).</p> <p>Primary safety objective:</p> <p>To compare <u>descriptively</u> the incidence of Major Bleeding (ISTH definition) in the edoxaban group against the VKA group in the period from date of first intake of study medication to Day 90/EOT.</p> <p>Secondary objectives:</p> <p>In subjects undergoing catheter ablation of AF, to compare <u>descriptively</u> the edoxaban group against the VKA group, with</p>

regards to the incidence of the following **efficacy endpoints** as listed below:

- Composite of all-cause death, stroke (ischemic, hemorrhagic, or undetermined, according to alternative definition (1); see Section 7.4.2. for details) and Major Bleeding (ISTH definition)
- Composite of stroke (ischemic, hemorrhagic, or undetermined) systemic embolic events (SEE), and cardiovascular (CV) mortality
- Composite of stroke (ischemic, hemorrhagic, or undetermined) SEE, and all-cause mortality
- Composite of stroke (ischemic, hemorrhagic, or undetermined) and transient ischemic attack (TIA)
- Stroke (ischemic, hemorrhagic, or undetermined)
- Stroke (ischemic)
- Stroke (hemorrhagic)
- Stroke (undetermined)
- SEE
- TIA
- Fatal stroke (ischemic, hemorrhagic, or undetermined)
- Non-fatal stroke (ischemic, hemorrhagic, or undetermined)
- Disabling stroke (ischemic, hemorrhagic, or undetermined)
- Non-disabling stroke (ischemic, hemorrhagic, or undetermined)

To compare descriptively the edoxaban group against the VKA group, with regards to the incidence of the following **safety endpoints** as listed below:

- Major Bleeding (defined by Thrombolysis in Myocardial Infarction [TIMI], Bleeding Academic Research Consortium [BARC] 2 or higher)
 - Major and Clinically Relevant Non-Major (CRNM) Bleeding (ISTH definition)
 - CRNM Bleeding (ISTH definition)
 - Minor Bleeding (ISTH definition)
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- Any Bleeding
 - Intracranial hemorrhage (ICH)
 - Life-threatening bleeding
 - Fatal Major Bleeding (ISTH definition)
 - Non-fatal Major Bleeding (ISTH definition)
 - Fatal Major Bleeding (defined by TIMI, BARC [2 or higher])
 - Non-fatal Major Bleeding (defined by TIMI, BARC [2 or higher])
 - Safety parameters such as adverse events (AEs), serious adverse events (SAEs), laboratory parameters, electrocardiogram (ECG) and vital signs.

Other objectives:

To compare descriptively the edoxaban group against the VKA group, with regards to the following:

- Relevant Health Economics Outcome Research (HEOR) parameters:
 - Number of subjects with cancellation of the ablation procedure due to inadequate anticoagulation
 - Number of hospital admissions due to CV causes (beyond ablation procedure), including but not limited to overall, for bleeding, SEE, venous thrombosis, etc. Remark: Hospital admissions due to CV causes include, but are not limited to Emergency Department (ED), Intensive Care Unit (ICU), CV ward.
 - Mean length of stay associated with the different type of hospital admissions, such as ED, ICU and CV wards
 - Additional outpatient physician or nurse visits that are CV event related outside scheduled visits as defined by study protocol
- Silent cerebral lesions (SCL) as defined by Diffusion Weighted Magnetic Resonance Imaging (DW-MRI) post ablation procedure (at preselected centers)
- Cardiac markers

Study Design:	This is a multinational prospective, randomized, open-label, blinded endpoint evaluation (PROBE) parallel group phase 3b study comparing edoxaban vs. VKA in subjects undergoing catheter ablation of non-valvular AF. After Screening and randomization,
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eligible subjects receive 21 days (+7) anticoagulation before being assessed for suitability for the catheter ablation procedure. Subjects will receive 90 days anticoagulation post-procedure and are then followed-up after an additional 30 days. In all subjects, key demographic and risk characteristics of both stroke and bleeding (for example, CHA₂DS₂-VASc score, HAS-BLED, type of AF, presence of coronary artery disease (CAD), heart failure (HF), diabetes mellitus (DM), and hypertension) will be collected. Subjects will be randomized in a 2:1 ratio to edoxaban vs. VKA into one of the two study arms as described below.

Edoxaban study arm

Subjects will be required to complete at least 21 (up to +7) days of anticoagulation with edoxaban. Subjects receiving anticoagulants at the time of enrollment will be switched to edoxaban (the switching procedure will follow the edoxaban label and is described in Section 5.2.1.3). It is mandatory that in the pre-ablation period, the once-daily dose of edoxaban is taken every day in the evening. Edoxaban can be taken with or without food.

If a subject has taken the study drug in the evening, the procedure can be performed in the morning of the next day. The interval between the last intake of edoxaban and the procedure must not exceed 18 hours. After the ablation, study medication must be re-started on the day of procedure but no earlier than 6 hours post-sheath removal and only once adequate hemostasis has been achieved.

Timing of the last dose of edoxaban prior to the catheter ablation procedure and the first dose after the procedure will be recorded in the electronic case report form (eCRF).

VKA study arm

Subjects enrolled in the VKA study arm will be required to complete at least 21 days (up to +7 days) of anticoagulation treatment with VKA. Subjects will take the VKA according to the direction of the Investigator. Every attempt will be made to bring subjects into the therapeutic target range (INR [International Normalized Ratio] 2.0-3.0) as fast as possible and to maintain the target INR range consistently.

INR will need to be measured frequently at the start of the study (unless a subject is receiving an unvarying VKA dose at the time of randomization) to record the time when INR reaches a level of ≥ 2.0 .

Before ablation, each subject must be in the INR range of 2.0-3.0 for the last 10 days prior to the catheter ablation. This will need to be documented by frequent INR measurements, at least once per week in the pre-ablation period. On the day of, or the day prior to, the

scheduled ablation procedure, subjects INR should be within the range 2.0-3.0. If INR is ≥ 1.5 and < 2.0 or if INR is > 3.0 and ≤ 3.5 the procedure may be performed at the Investigator's discretion. Otherwise, the subject is not eligible for performing the catheter ablation (the subject will be switched from study medication to standard of care and will enter the 30-day follow-up period).

During the catheter ablation procedure, VKA will be used without interruption and bridging with low molecular weight heparin (LMWH) will not be allowed at this time.

Transesophageal echocardiogram before catheter ablation

Transesophageal echocardiogram (TEE) or alternatively intra-cardiac echocardiogram will be performed before catheter ablation during the hospital stay related to the procedure or the day before to identify potential clots. If TEE or the intra-cardiac echocardiogram is positive, i.e., shows clots, the ablation procedure will be canceled and the subject will be switched from study medication to standard of care and will enter the 30-day follow-up period.

Anticoagulation during catheter ablation

According to standard of care and as recommended in current treatment guidelines (15) heparin should be administered (100 U/kg bolus) prior to or immediately following trans-septal puncture during AF ablation procedures and adjusted to achieve and maintain an activated clotting time (ACT) of 300-400 seconds. ACT levels should be checked at 15-20-minute intervals until therapeutic anticoagulation is achieved and then at 30-minute intervals for the duration of the procedure. Heparin anticoagulation will be partially reversed with protamine and sheaths removed at an ACT < 250 seconds.

Anticoagulation post catheter ablation

Following completion of the catheter ablation procedure, all subjects will continue receiving treatment within their study arm until Day 90 post-procedure.

At the End of Treatment

At Day 90 post-procedure, the subject will discontinue the study treatment completely and will be continued on any of the approved oral anti-coagulation (OAC) drugs or anticoagulation stopped according to standard of care per physician's discretion. Detailed switching protocols according to medication label will be provided.

All subjects regardless of their post-study treatment will have an additional 30-day safety follow-up period after which their participation in the study will be completed.

Study Duration:	Total for each subject 5-6 months. Pre-ablation treatment period of at least 21 days (up to +7 days). Post-ablation treatment period of 90 days (± 7 days) plus 30-day follow-up period (up to +5 days). Projected 16 months enrollment
Study Sites and Location:	It is planned to enroll approx. 560 subjects with 2:1 randomization ratio (edoxaban:VKA) by approximately 75 study sites located in Canada, Europe (Belgium, Czech Republic, France, Germany, Hungary, Italy, Netherlands, Poland, Spain, United Kingdom), Korea, and Taiwan to achieve approx. 450 subjects undergoing the catheter ablation procedure and completing the study.
Subject Eligibility Criteria:	<p><u>Inclusion criteria:</u></p> <ol style="list-style-type: none"> 1. Male or female at least 18 years of age with documented history of paroxysmal (lasting ≤ 7 days), persistent (lasting > 7 days but ≤ 12 months) or long-standing [long-lasting] persistent (> 12 months) non-valvular AF. Duration of AF can be confirmed by any electrical tracing or a recording in the subject's medical records (e.g., medical chart, hospital discharge summary). 2. Subject is eligible and is scheduled for either radio frequency (RF) or cryoballoon catheter ablation (both first and repeated procedure included). 3. Signed informed consent form (ICF). <p><u>Exclusion criteria:</u></p> <ol style="list-style-type: none"> 1. AF considered to be of a transient or reversible nature (such as in myocarditis, post-surgery, ionic disturbances, thyrotoxicosis, pneumonia, severe anemia etc.). 2. Subject post stroke, or with a systemic thromboembolic event within the past 6 months prior to randomization. 3. Subject has a thrombus in the left atrial appendage (LAA), left atrium (LA), left ventricle (LV), or aorta, or an intracardial mass. 4. Subject had a myocardial infarction (MI) within the 2 months prior to randomization or coronary artery bypass graft (CABG) surgery within 3 months prior to the randomization. 5. Subject has signs of bleeding, history of clinically-relevant bleeding according to ISTH, or conditions associated with high risk of bleeding such as past history of intracranial (spontaneous or traumatic), or spontaneous intraocular, spinal, retroperitoneal, or intra-articular bleeding; overt

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- gastrointestinal (GI) bleeding or active ulcer within the previous year; recent severe trauma, major surgery, or deep organ biopsy; active infective endocarditis; uncontrolled hypertension (blood pressure [BP] above 170/100 mmHg); or hemorrhagic disorder including known or suspected hereditary or acquired bleeding or coagulation disorder in the last 12 months prior to randomization.
6. Subjects with mechanical heart valves, subjects with moderate to severe mitral stenosis and subjects who have new implantation (within 3 months prior to randomization) of a bioprosthetic heart valve, with or without AF.
 7. Subjects with a history of LAA occlusion/exclusion (either by surgery or by a procedure).
 8. Subjects with any contraindication for edoxaban, VKA, LMWH, heparin therapy including known allergies, hypersensitivity, or intolerance to any component of these drugs or its excipients.
 9. Subjects receiving dual antiplatelet therapy (DAPT, i.e., aspirin and P2Y₁₂ antagonist) or planned to receive DAPT during the study.
 10. Unfractionated heparin (UFH), low molecular weight heparins (LMWH; enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), and oral anticoagulants (warfarin, dabigatran etexilate, rivaroxaban, apixaban etc.) cannot be used concomitantly to study medication. Any bridging with LMWH around the CA procedure is prohibited. During the CA procedure, UFH will be used according to standard of care to achieve ACT of 300 to 400 sec. Subjects who require chronic use of medicines affecting hemostasis such as higher doses of aspirin (acetylsalicylic acid [ASA]) (ASA up to 100 mg per day allowed) or chronic oral or parenteral intake of non-aspirin non-steroidal anti-inflammatory drugs (NSAID) on ≥ 4 days/week (use of NSAIDs via other routes is not restricted).
 11. Subjects with active liver disease or persistent (confirmed by repeat assessments at least a week apart) elevation of liver enzymes/bilirubin:
 - Alanine transaminase (ALT) or aspartate transaminase (AST) ≥ 2 times the upper limit of normal (ULN)
 - Total bilirubin (TBL) ≥ 1.5 times the ULN (subjects whose elevated TBL is due to known Gilbert's syndrome may be included in the study)
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- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
12. Subjects with kidney failure (calculated creatinine clearance [CrCL] <15 mL/min).
 13. Subjects with hemoglobin <10 g/dL or platelet count <100,000 cells/ μ L or white blood cell (WBC) count <3000 cells/ μ L.
 14. Subjects with pre-planned invasive diagnostic or therapeutic procedures/interventions (other than endoscopy) during the study period in which bleeding is anticipated.
 15. Participation in any other interventional trial (subjects who received any investigational drug or device within 30 days prior to randomization, or plan to receive such investigational therapy during the study period).
 16. Previous randomization in this study.
 17. Female subjects of childbearing potential without using highly effective contraception (female of childbearing potential is defined as one who has not been postmenopausal for at least one year, or has not been surgically sterilised, or has not had a hysterectomy at least three months prior to the start of this study). Females taking oral contraceptives should have been on therapy for at least three months. Adequate contraceptives include: Combined (estrogen and progestogen containing) oral, intravaginal or transdermal hormonal contraception associated with inhibition of ovulation; progestogen-only oral, injectable or implantable hormonal contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomized partner; sexual abstinence.
 18. Pregnant or breast-feeding subjects.
 19. Subjects with the following diagnoses or situations:
 - Active cancer undergoing chemotherapy, radiation or major surgery within the next 5 months
 - Significant active/uncontrolled concurrent medical illness
 - Life expectancy <6 months.
 20. Subjects who are unlikely to comply with the protocol (e.g., uncooperative attitude, inability to return for subsequent visits, and/or otherwise considered by the Investigator to be unlikely to complete the study).
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21. Subjects with a known drug or alcohol dependence within the past 12 months prior to randomization as judged by the Investigator.
 22. Subjects with any condition that, in the opinion of the Investigator, would place the subject at increased risk of harm if he/she participated in the study.
 23. Planned procedure using laser catheter ablation or other forms of catheter ablation different from RF or cryoballoon (i.e. high intensity focused ultrasound [HIFU], microwaves, hot balloon, etc).
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Dosage Form, Dose,
and Route of
Administration:

Edoxaban: 60 mg and 30 mg provided as film coated tablets for oral use (30 mg or 15 mg as transition medication if applicable).

The dose of edoxaban is 60 mg once-daily and will be reduced to 30 mg once-daily, if the subject has one of the following:

- Moderate or severe renal impairment ($\text{CrCL} \geq 15$ to ≤ 50 mL/min as calculated using the Cockcroft-Gault formula)
- Low body weight (≤ 60 kg)
- Receives one of the following concomitant P-gp inhibitors: ciclosporin, dronedarone, erythromycin, ketoconazole.
Remark: In EU countries, according to the Summary of Product Characteristics (SmPC) concomitant use of edoxaban with cyclosporine, dronedarone, erythromycin, or ketoconazole requires dose reduction to 30 mg once-daily. Concomitant use of edoxaban with quinidine, verapamil, or amiodarone does not require dose reduction

It is mandatory that in the pre-ablation period, the once-daily dose of edoxaban is taken every day in the evening. Edoxaban can be taken with or without food.

VKA: Oral VKA, as pre-defined per country, with once-daily dosing for target INR between 2.0-3.0, inclusive. Subjects will take the VKA once-daily according to the direction of the Investigator.

VKA is supplied as commercially available tablets of the preferred VKA for each selected country participating in the study, being either:

- Warfarin: 1 and 2.5 mg tablets.
 - Phenprocoumon: 3 mg tablets.
 - Fluindione: 20 mg tablets (exclusive to France).
 - Acenocoumarol: 4 mg tablets.
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The Investigator monitors the INR and adjusts the VKA dose to maintain the INR within target. It is the Investigator's responsibility to collect INR assessments and record these throughout the study.

Study Endpoints:

Primary efficacy endpoint

Composite of all-cause death, stroke (ischemic, hemorrhagic, or undetermined), and Major Bleeding (ISTH), analyzed as time to first occurrence of any component

Primary safety endpoint

Major Bleeding (ISTH), analyzed as time to first occurrence of Major Bleeding

Secondary endpoints

Efficacy:

- Composite of all-cause death, stroke (ischemic, hemorrhagic, or undetermined, according to alternative definition (1); see Section 7.4.2 for details) and Major Bleeding (ISTH definition)
- Composite of stroke (ischemic, hemorrhagic, or undetermined) SEE, and CV mortality
- Composite of stroke (ischemic, hemorrhagic, or undetermined) SEE, and all-cause mortality
- Composite of stroke (ischemic, hemorrhagic, or undetermined) and TIA
- Stroke (ischemic, hemorrhagic, or undetermined)
- Stroke (ischemic)
- Stroke (hemorrhagic)
- Stroke (undetermined)
- SEE
- TIA
- Fatal stroke (ischemic, hemorrhagic, or undetermined)
- Non-fatal stroke (ischemic, hemorrhagic, or undetermined)
- Disabling stroke (ischemic, hemorrhagic, or undetermined)
- Non-disabling stroke (ischemic, hemorrhagic, or undetermined)

Safety:

- Major Bleeding (defined by TIMI, BARC [2 or higher])
- Major and CRNM Bleeding (ISTH definition)
- CRNM Bleeding (ISTH definition)
- Minor Bleeding (ISTH definition)
- Any Bleeding
- ICH
- Life-threatening bleeding
- Fatal Major Bleeding (ISTH definition)
- Non-fatal Major Bleeding (ISTH definition)
- Fatal Major Bleeding (defined by TIMI, BARC [2 or higher])
- Non-fatal Major Bleeding (defined by TIMI, BARC [2 or higher])
- Safety parameters such as AEs, SAEs, laboratory parameters, ECG and vital signs.

All adjudicated endpoints are analyzed as time to first occurrence of any of its components.

For all specific endpoints blindly adjudicated by the Clinical Endpoints Committee (CEC), the CEC's interpretation prevails and is used in the statistical analyses.

Other endpoints:

- Relevant HEOR parameters:
 - Number of subjects with cancellation of the ablation procedure due to inadequate anticoagulation
 - Number of hospital admissions due to CV causes (beyond ablation procedure), including but not limited to overall, for bleeding, SEE, venous thrombosis, etc. Remark: Hospital admissions due to CV causes include, but are not limited to ED, ICU, CV ward.
 - Mean length of stay associated with the different type of hospital admissions, such as ED, ICU and CV wards
 - Additional outpatient physician or nurse visits that are CV event related outside scheduled visits as defined by study protocol

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- SCL as defined by DW-MRI post ablation procedure (at preselected centers)
 - Cardiac markers
-

Planned Sample Size: The primary endpoint will be the incidence of a composite of all-cause death, stroke (ischemic stroke, hemorrhagic stroke, or undetermined stroke), and Major Bleeding events (ISTH definition) during the period from the end of the catheter ablation procedure to Day 90/EOT. A rate of up to 3% of the combined primary endpoint can be expected in the VKA arm as observed from published studies and retrospective analyses (for more details, please refer to Section 10.7).

Based upon this low predicted rate, a formal sample size determination based on non-inferiority or superiority of edoxaban versus VKA is not feasible. The sample size is planned based upon the primary composite endpoint to include an adequate number of subjects that will provide the expected incidence rates on the primary endpoint. Therefore, the plan is to include 450 subjects in the Per Protocol (PP) analysis set, i.e. subjects who have undergone an ablation procedure and without any major protocol violation.

In order to achieve this, approximately 560 subjects will need to be enrolled in the study. The study will be stopped once the number of 450 subjects belonging to the PP analysis set is reached.

Statistical Analyses: The following analysis sets are defined:

The *Intention-to-treat (ITT) analysis set* consists of all randomized subjects irrespective whether they received a single dose of study medication or not.

The *modified Intention-to-treat (mITT) analysis set* consists of all randomized subjects who received at least one dose of study medication.

The *Per Protocol (PP) analysis set* consists of all randomized subjects who received at least one dose of study medication and do not have any of the following major protocol violations:

- Not undergoing a catheter ablation
- No AF
- Known contraindication for OAC
- A major violation of the inclusion criteria
- A major violation of the exclusion criteria

The list of major protocol violations will be described in the statistical analysis plan (SAP) and finalized before data base lock.

The *Safety (SAF) analysis set* consists of all randomized subjects who received at least one dose of study medication.

Definition of terms:

‘*Overall Study Period*’: This period is defined as the time from the reference date (date and time of randomization or date and time of first dose of study medication) to Day 90/EOT.

‘*Overall Study Period + 30 days*’: This period is defined as the time from the reference date (date and time of randomization or date and time of first dose of study medication) to Day 90/EOT + 30 days.

‘*Post-ablation Study Period*’: This period is defined as the time from the end of the catheter ablation procedure to Day 90/EOT.

‘*Post-ablation Study Period + 30 days*’: This period is defined as the time from the end of the catheter ablation procedure to Day 90/EOT + 30 days.

Planned Analyses:

According to the objectives of this study, the statistical analysis should be interpreted in a purely exploratory-descriptive way. No formal confirmatory statistical testing is planned.

The analysis set and analysis period to be used for the main analysis of the various adjudicated endpoints is presented below:

Endpoint(s)	primary analysis set	primary analysis period
Primary	PP	post-ablation period
Primary safety	mITT	overall study period
Secondary efficacy	PP	post-ablation period
Secondary safety	mITT	overall study period

For each of the primary and secondary adjudicated endpoints, appropriate summary statistics (e.g. event rate) including 95% confidence interval (CI) will be provided.

For each of the endpoints, the time from reference date to the first occurrence of an event (based on CEC adjudication), is analyzed using a Cox proportional hazard model with treatment regimen as a factor, to provide point estimates and 95% CI for the hazard ratio (HR). Depending on the analysis period used in the statistical analysis,

subjects without an occurrence of an event will be censored at the last date of the analysis period or at the last date of known outcomes status. The latter is determined on an individual basis for subjects with incomplete follow-up.

For time to first event analyses based on any of the study periods defined above, cumulative event rates over time are summarized using the Kaplan-Meier method.

To evaluate the robustness of the main analyses, the analysis will be repeated using the mITT, ITT and/or PP analysis set. In addition, the statistical results based on the following analysis periods: 'post-ablation study period + 30 days' and 'overall study period + 30 days' will be presented.

All details of the statistical analysis will be described in a SAP.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ACT	Activated clotting time
AE	Adverse event
AESI	Adverse event of special interest
AF	Atrial fibrillation
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ARC	Academic Research Consortium
ASA	Acetylsalicylic acid
AST	Aspartate transaminase
BARC	Bleeding Academic Research Consortium
BP	Blood pressure
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CEC	Clinical Events Committee
CHADS ₂	Congestive heart failure, Hypertension, Age, Diabetes, previous Stroke risk score
CI	Confidence interval
CNS	Central nervous system
COX	Cyclooxygenase
CrCL	Creatinine clearance
CRF	Case report form
CRNM	Clinically relevant non-major
CRO	Contract Research Organization
cTn-hs	cardiac troponin high sensitivity
CV	Cardiovascular
DAPT	Dual Antiplatelet Therapy (e.g., aspirin and P2Y ₁₂ antagonist)
DM	Diabetes mellitus
DSE	Daiichi Sankyo Europe
DSMB	Data and Safety Monitoring Board
DVT	Deep vein thrombosis
DWI	Diffusion weighted imaging
DWI-FLAIR	Diffusion weighted imaging fluid attenuated inversion recovery
DW-MRI	Diffusion weighted magnetic resonance imaging
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
ED	Emergency department
EDC	Electronic data capture
EHRA	European Heart Rhythm Association
EOT	End-of-Treatment
EU	European Union

ABBREVIATION	DEFINITION
EudraCT	European union drug regulating authorities clinical trials
FXa	Factor Xa
GCP	Good Clinical Practice (refers to ICH)
GI	Gastrointestinal
GM	Grey matter
HEOR	Health Economics Outcome Research
HF	Heart failure
HIFU	High intensity focused ultrasound
HR	Hazard ratio
IB	Investigator Brochure
IC	Informed consent
ICF	Informed Consent Form
ICH	Intracranial hemorrhage
ICU	Intensive Care Unit
ID	Identification
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Hemostasis
ITT	Intent-to-treat (analysis set)
IXRS	Interactive web/voice response system
LA	Left atrium
LAA	Left Atrial Appendage
LMWH	Low molecular weight heparin
LV	Left ventricle
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
mITT	Modified ITT (analysis set)
MRI	Magnetic resonance imaging
mRS	modified Rankin Scale
NOAC	Non-vitamin K antagonist oral anticoagulant
NSAID	Non-steroidal anti-inflammatory drug
NT-proBNP	N-terminal fragment B-type natriuretic peptide
OAC	Oral anticoagulant
PD	Pharmacodynamic
PE	Pulmonary embolism
P-gp	P-glycoprotein
PK	Pharmacokinetic
PP	Per protocol
PROBE design	Prospective, Randomized, Open-label study with Blinded Evaluation of endpoints
RF	Radio frequency

ABBREVIATION	DEFINITION
SAE	Serious adverse event
SAF	Safety (analysis set)
SAP	Statistical analysis plan
SCE	silent cerebral events
SCL	silent cerebral lesions
SEE	Systemic embolic events
SmPC	Summary of Product Characteristics
SOP	Standard operating procedures
SUSAR	Suspected, unexpected, serious adverse reaction
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TEE	Transesophageal echocardiogram
TIA	Transient ischemic attack
TIMI	Thrombolysis in Myocardial Infarction
TTR	Time in therapeutic range
ULN	Upper limit of normal
VKA	Vitamin K antagonist
vs	Versus
VTE	Venous thromboembolism
WBC	White blood cells

1. INTRODUCTION

1.1. Background

Atrial fibrillation (AF) is the most common arrhythmia in adults, affecting 0.5% to 1% of the total population and >8% of subjects older than 80 years. Subjects suffering from AF are at an increased risk of stroke, progressing heart failure and sudden death. Catheter ablation as a method of treating AF is more and more frequently performed in clinical practice due to its effectiveness on AF-related symptoms and quality of life (3). However, this procedure is associated with a significant thromboembolic risk during and shortly after the procedure. The causes of thromboembolic events during and after the ablation are multiple and as such, the use of oral anticoagulants during the catheter ablation procedure is therefore warranted (2).

Vitamin K antagonists (VKAs) have been traditionally used to prevent procedure-related thromboembolism (4). The traditional anticoagulation approach is to interrupt administration of an oral VKA and use heparin bridging. More recently, studies have indicated that uninterrupted anticoagulation may be safer and more effective (5). Current AF guidelines recommend consideration of uninterrupted oral anticoagulation for patients undergoing catheter ablation (2). In a European Heart Rhythm Association survey, 71.6% of respondents reported using the uninterrupted VKA strategy for catheter ablation (6).

Non-vitamin K oral anticoagulants (NOACs) offer important advantages over VKA beyond their ease of administration, such as fewer interactions and no need of laboratory monitoring, and have become widely available and represent an attractive alternative in this setting.

1.2. Description of Investigational Product

Edoxaban tosylate (DU-176b) is an antithrombotic agent, an orally active, selective, direct, and reversible inhibitor of Factor Xa (FXa), manufactured by Daiichi Sankyo Co., Ltd., Japan. Inhibition of FXa in the coagulation cascade prolongs clotting time and potentially reduces the risk of spontaneous or induced thrombus formation.

International non-proprietary name: Edoxaban (DU-176) refers to the anhydrous free base of edoxaban tosylate. Subjects are given edoxaban tosylate (a monohydrate salt) but all doses and plasma concentrations are expressed in terms of edoxaban, the anhydrous free base.

For simplicity, this protocol uses the term “edoxaban” to refer to either or both forms.

1.2.1.1. Nonclinical Studies

In nonclinical studies, edoxaban showed excellent potential as an antithrombotic agent. Results of non-clinical toxicology studies do not indicate any major clinically concerning adverse effects in study animals exposed to edoxaban. Additional details are available in the edoxaban Investigator's Brochure (IB) (7).

1.2.1.2. Clinical Experience

Edoxaban was initially approved in Japan for the prevention of venous thromboembolism (VTE) in patients undergoing any of the following orthopedic procedures on the lower limb: total knee

replacement, total hip replacement, and hip fracture surgery and then subsequently for the prevention of ischemic stroke and systemic embolism in patients with non-valvular AF; treatment and recurrence prevention of VTE. In 2015, edoxaban was approved in the European Union (EU) for the prevention of stroke and systemic embolism in adult patients with nonvalvular AF with one or more risk factors (such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA), and for the treatment and prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE). Similar indications were also approved in the United States and other countries and regions.

The efficacy and safety of edoxaban for reducing the risk of stroke and systemic embolic events (SEEs) in subjects with non-valvular AF was demonstrated in a large pivotal Phase 3 study (ENGAGE AF-TIMI 48) (1). Similarly, the efficacy and safety of edoxaban for the treatment of VTE, including DVT and PE, and the prevention of recurrent VTE was demonstrated in the Phase 3 Hokusai VTE study (8).

Features of the Hokusai VTE and ENGAGE AF-TIMI 48 studies are summarized in [Table 1.1](#).

Table 1.1: Summary of the Hokusai VTE and ENGAGE AF-TIMI 48 Studies

Study Population	Median Duration of Treatment	Treatment Groups	N	Primary Efficacy Outcome		Primary Safety Outcome	
				Endpoint	HR (95% CI) Edoxaban vs Warfarin	Endpoint	HR (95% CI) Edoxaban vs Warfarin
Hokusai VTE (acute VTE)	0.7 years	Edoxaban 60 mg	4118	Recurrent VTE	0.89 (0.70, 1.13) mITT, overall study period	Major + CRNM Bleeding	0.81 (0.705, 0.936) mITT, on-treatment period
		Warfarin	4122				
ENGAGE AF-TIMI 48 (non-valvular AF)	2.5 years	Edoxaban High Dose Regimen*	7012	Stroke and SEE	0.79 (0.63, 0.99) mITT, on-treatment period	Major Bleeding	0.80 (0.71, 0.91) mITT, on-treatment period
		Edoxaban Low Dose Regimen**	7002		1.07 (0.87, 1.31) mITT, on-treatment period		0.47 (0.41, 0.55) mITT on-treatment period
		Warfarin	7012		-		-

Abbreviations: AF = atrial fibrillation; CI = confidence interval; CRNM = clinically relevant non-major; HR = Hazard Ratio; SEE = systemic embolic event; vs = versus; VTE = venous thromboembolism; mITT = modified intention-to-treat; N = number of treated subjects

*High Dose Regimen = 60 mg edoxaban once-daily with reduction to 30 mg once-daily in subjects with low body weight, moderate renal impairment, or specified concomitant medications;

**Low Dose Regimen = 30 mg edoxaban once-daily with reduction to 15 mg once-daily in subjects with low body weight, moderate renal impairment, or specified concomitant medications.

Other completed studies include Phase 1 clinical pharmacology studies, Phase 2 dose-ranging studies in subjects with non-valvular AF and subjects undergoing lower-extremity orthopedic surgery, and Phase 3 studies in subjects undergoing lower-extremity orthopedic surgery.

In the course of the edoxaban clinical development program, over 23,500 subjects have been given edoxaban encompassing over 34,100 subject-years of exposure. The safety and efficacy of edoxaban has been evaluated in the following programs:

- Phase 1 studies (including 1627 subjects from pharmacokinetic (PK)-pharmacodynamic (PD) studies, PK in subjects with renal impairment, and drug-drug interaction studies): Results of these studies have shown that edoxaban is rapidly absorbed with rapid onset of

action and the dose concentration relationship is generally linear. The mean terminal half-life is between 10-14 hours. The PD effect as measured by anti-Xa activity or inhibition of FXa activity lasts for 24 hours. Dose-related increases in PK concentrations and anti-thrombotic activity were observed, as measured by anti-Xa activity. The bioavailability is ~60% and 50% of the absorbed drug is excreted by renal clearance. The absorption, distribution, metabolism, and excretion are also mediated through the P-glycoprotein (P-gp) transport system and drugs with P-gp inhibitory effects may alter edoxaban exposure.

- Phase 2 studies in AF subjects (including 1,973 subjects): These studies primarily evaluated safety of different dose regimens of edoxaban with approximately 12 weeks of treatment. Results of these studies showed that the twice a day regimen had higher bleeding than once-daily regimen of edoxaban. Consequently, the once-daily regimen of edoxaban was tested in the subsequent Phase 3 trials.
- Phase 3 AF pivotal trial (ENGAGE AF-TIMI 48) involving 21,026 treated subjects with a median follow-up of 2.8 years (median treatment 2.5 years). Two once-daily regimens of edoxaban were compared with warfarin for the prevention of stroke and systemic embolism in patients with non-valvular AF. Both regimens were non-inferior to warfarin for the prevention of stroke and systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular (CV) causes. Edoxaban has been approved for marketing in the United States and EU for this indication.
- Phase 2/3 VTE prophylaxis studies in subjects undergoing orthopedic surgery (including 3,678 subjects). Edoxaban has been approved for marketing in Japan for this indication.
- Phase 3 VTE pivotal trial (Hokusai-VTE) involving 8,240 treated subjects. Edoxaban administered once-daily after initial treatment with heparin was non-inferior to standard therapy and caused significantly less bleeding in patients with VTE. Edoxaban has been approved for marketing in the US and EU for this indication.

1.2.1.3. Dose Rationale

Based on the results of the ENGAGE AF-TIMI 48 and Hokusai-VTE studies, an edoxaban dose that is considered as safe and effective for patients with AF or VTE and is included in the label (prescribing information) has been selected for this trial. Edoxaban has not been evaluated in patients with AF undergoing catheter ablation of non-valvular AF but no evidence exists suggesting further that dose adaptation is required.

1.3. Risks and Benefits for Study Subjects

Atrial fibrillation (AF) is the most frequent sustained arrhythmia in clinical practice. Catheter ablation of AF has been established as an effective therapy for the treatment of symptoms in these patients (3). However, this procedure is associated with a significant thromboembolic risk. In a recent world-wide survey (9), the overall incidence of major complications of cardiac ablation was 4.5% and the death rate was 0.15%. Tamponade was the most frequent complication (1.31%), followed by total femoral pseudoaneurysm (0.93%), TIAs (0.71%), total artero-venous fistulae (0.54%), pulmonary vein stenosis requiring intervention (0.29%) and stroke (0.23%). The causes of thromboembolic events during and after the ablation are multiple and include (I) char formation at the catheter tip, (II) mobilization of pre-existing left atrial thrombi, (III) thrombus formation in left atrial sheaths, (IV) the thrombogenic potential of left atrial endocardial lesions, and (V) electrical cardioversion during the procedure.

Anticoagulation therapy is therefore required before, during, and for a period after the procedure (as defined by guidelines), and may be continued indefinitely in patients with ongoing risk factors for stroke (Congestive heart failure, Hypertension, Age, Diabetes, previous Stroke risk score [CHADS_2] ≥ 1 or $\text{CHA}_2\text{DS}_2\text{-VASc}$ ≥ 2).

Traditionally, VKAs (eg, coumarins and indanediones) are used as anticoagulant medications (sometimes with enoxaparin administered as a ‘bridge’ during the procedure) to reduce the risk of stroke and thromboembolic complications in subjects with AF undergoing catheter ablation. Guidelines recommend uninterrupted VKA therapy, for example with warfarin, dosed to an International Normalized Ratio (INR of 2.0–2.5). However, these VKAs (anticoagulant agents) are indirect thrombin inhibitors which act by blocking the vitamin K-dependent liver production of plasma clotting factors, prothrombin (Factor II), and Factors VII, IX, and X. The use of warfarin is complicated by several inherent problems, including a delayed onset of antithrombotic action, narrow therapeutic index that requires close anticoagulation monitoring using the INR, unpredictable and variable pharmacological response, and mandatory regular laboratory monitoring to control its anticoagulant effect and minimize the risk of serious bleeding. Furthermore, numerous drugs, certain dietary supplements, alcohol, and some foods markedly affect warfarin dose response. This is in addition to the finding that warfarin use increases both the risk of developing intra cerebral hemorrhage and mortality.

However, as VKAs may be difficult to manage, the fixed-dose NOACs are increasingly used instead of VKAs and their use in patients undergoing ablation is therefore of interest also.

The NOACs offer the benefits of predictable effect without need for monitoring, fewer food and drug interactions, shorter plasma half-life, and an improved efficacy/safety ratio. Several small, non-randomized, observational studies and meta-analyses (e.g. 10, 11, 12, 13, 14) have suggested a similar safety and efficacy profile for the direct FXa inhibitors rivaroxaban and apixaban, and the direct thrombin inhibitor dabigatran, compared to warfarin.

In a sub-analysis of the large, randomized ROCKET AF study, a relatively small group of patients undergoing catheter ablation or cardioversion had similar outcomes when receiving either rivaroxaban or warfarin (16). The use of rivaroxaban was investigated in patients undergoing catheter ablation for non-valvular AF in the VENTURE AF study, which showed similar safety

outcomes with uninterrupted oral rivaroxaban and uninterrupted standard VKA therapy. The incidence of Major Bleeding events was very low in both treatment groups, and remained consistent throughout the study period (3).

Therefore, there exists a need for a safer, more effective, and easily manageable oral anticoagulant (OAC) agent for the prevention of acute stroke in subjects with AF who are scheduled for catheter ablation. It is expected that edoxaban will provide comparable efficacy to warfarin, but with a predictable and faster antithrombotic response and with no need for laboratory monitoring.

Edoxaban is a selective FXa inhibitor with rapid onset of action and predictable and excellent antithrombotic properties. In more than 35,000 subjects treated to date, edoxaban appears to be well tolerated up to a dose of 90 mg daily, with expected transient and manageable bleeding adverse events (AEs) and transient and reversible liver enzyme and bilirubin elevations.

2. STUDY OBJECTIVES AND HYPOTHESES

2.1. Study Objectives

2.1.1. Primary Objectives

Primary Efficacy Objective:

To compare descriptively the incidence of the composite of all-cause death, stroke (ischemic, hemorrhagic, or undetermined) and Major Bleeding (International Society on Thrombosis and Hemostasis [ISTH] definition) in the edoxaban group against the VKA group in subjects undergoing catheter ablation of AF, in the period from the end of the catheter ablation procedure to Day 90/End-of-Treatment (EOT).

Primary Safety Objective:

To compare descriptively the incidence of Major Bleeding (ISTH definition) in the edoxaban group against the VKA group in the period from the date of first intake of study medication to Day 90/EOT.

2.1.2. Secondary Objectives

In subjects undergoing catheter ablation of AF, to compare descriptively the edoxaban group against the VKA group, with regards to the incidence of the following **efficacy endpoints** as listed below:

- Composite of all-cause death, stroke (ischemic, hemorrhagic, or undetermined, according to alternative definition (1); see Section 7.4.2. for details) and Major Bleeding [ISTH definition]
- Composite of stroke (ischemic, hemorrhagic, or undetermined), SEE, and CV mortality
- Composite of stroke (ischemic, hemorrhagic, or undetermined) SEE, and all-cause mortality
- Composite of stroke (ischemic, hemorrhagic, or undetermined) and TIA
- Stroke (ischemic, hemorrhagic, or undetermined)
- Stroke (ischemic)
- Stroke (hemorrhagic)
- Stroke (undetermined)
- SEE
- TIA
- Fatal stroke (ischemic, hemorrhagic, or undetermined)
- Non-fatal stroke (ischemic, hemorrhagic, or undetermined)
- Disabling stroke (ischemic, hemorrhagic, or undetermined)
- Non-disabling stroke (ischemic, hemorrhagic, or undetermined)

To compare descriptively the edoxaban group against the VKA group, with regards to the incidence of the following **safety endpoints** as listed below:

- Major Bleeding (defined by Thrombolysis in Myocardial Infarction [TIMI], Bleeding Academic Research Consortium [BARC] (2 or higher))
- Major and Clinically Relevant Non-Major (CRNM) Bleeding (ISTH definition)
- CRNM Bleeding (ISTH definition)
- Minor Bleeding (ISTH definition)
- Any Bleeding
- Intracranial hemorrhage (ICH)
- Life-threatening bleeding
- Fatal Major Bleeding (ISTH definition)
- Non-fatal Major Bleeding (ISTH definition)
- Fatal Major Bleeding (defined by TIMI, BARC [2 or higher])
- Non-fatal Major Bleeding (defined by TIMI, BARC [2 or higher])
- Safety parameters such as AEs, serious adverse events (SAEs), laboratory parameters, electrocardiogram (ECG) and vital signs.

2.1.3. Other Objectives

To compare descriptively the edoxaban group against the VKA group, with regards to the following:

- Relevant Health Economics Outcome Research (HEOR) parameters:
 - Number of subjects with cancellation of the ablation procedure due to inadequate anticoagulation
 - Number of hospital admissions due to CV causes (beyond ablation procedure), including but not limited to overall, for bleeding, SEE, venous thrombosis, etc. (Remark: Hospital admissions due to CV causes include, but are not limited to Emergency Department (ED), Intensive Care Unit (ICU), CV ward.)
 - Mean length of stay associated with the different type of hospital admissions, such as ED, ICU and CV wards
 - Additional outpatient physician or nurse visits that are CV event related outside scheduled visits as defined by study protocol
- Silent cerebral lesions as defined by diffusion weighted magnetic resonance imaging (DW-MRI) post ablation procedure (at preselected centers)
- Cardiac markers.

3. STUDY DESIGN

3.1. Overall Plan

This is a multinational, prospective, randomized, open-label, blinded endpoint evaluation (PROBE) parallel group phase 3b study comparing edoxaban vs. VKA in subjects undergoing catheter ablation of non-valvular AF. In all subjects key demographic and risk characteristics of both stroke and bleeding (for example, CHA₂DS₂-VASc score, HAS-BLED, type of AF, presence of coronary artery disease (CAD), heart failure (HF), diabetes mellitus (DM), and hypertension) will be collected.

It is planned to enroll approx. 560 subjects at 75 study sites located in Canada, Europe (Belgium, Czech Republic, France, Germany, Hungary, Italy, Netherlands, Poland, Spain, United Kingdom), Korea, and Taiwan to achieve approx. 450 subjects undergoing the catheter ablation procedure and completing the study. Enrollment is anticipated to occur over a period of approximately 16 months.

Subjects eligible to participate must provide written informed consent (IC) before randomization or any study-specific procedures are performed. Once the informed consent form (ICF) has been signed, eligible subjects are randomized without delay to one of the two study arms (2:1 edoxaban vs. VKA)

Enrollment of subjects will occur between 21 to 28 days before the cardiac ablation procedure. The baseline visit may be split into two steps as per local requirements. In the pre-ablation treatment period, an optional visit may occur for those patients who do not have the option of INR measurement in an ambulatory setting.

Subjects will be required to have completed at least 21 (up to +7) days of anticoagulation with study treatment (edoxaban or VKA) prior to the catheter ablation visit / periprocedural visit (Day 0). Subjects randomized to VKA must be in the INR range of 2.0-3.0 for the last 10 days prior to the catheter ablation visit / periprocedural visit (Day 0). This will need to be documented by frequent INR measurements, at least once per week in the pre-ablation period. On the day of, or the day prior to, the scheduled ablation procedure, subjects INR should be within the range 2.0-3.0. If INR is ≥ 1.5 and < 2.0 or if INR is > 3.0 and ≤ 3.5 the procedure may be performed at the Investigator's discretion. Otherwise, the subject is not eligible for performing the catheter ablation (the subject will be switched from study medication to standard of care and will enter the 30-day follow-up period).

Transesophageal echocardiogram (TEE) or alternatively intra-cardiac echocardiogram will be performed before catheter ablation during the hospital stay related to the procedure or the day before to identify potential clots. If TEE or the intra-cardiac echocardiogram is positive, i.e., shows clots, the ablation procedure will be canceled and the subject will be switched from study medication to standard of care and will enter the 30-day follow-up period.

The randomized treatment regimens are continued for 90 days, when the scheduled EOT is reached. In subjects randomized to VKA, when after ablation, the subjects' anticoagulation is more constant, the frequency of INR measurements may be lower than in the pre-ablation period. However, in the post-ablation period, at least monthly INR controls are required. Subject clinical visits are planned at 30, and 90 days after cardiac ablation. A telephone assessment (personal visit as an alternative option) will be made at Day 60. All randomized subjects who are on study

medication (study edoxaban or VKA) at 90 days, will have a post-treatment contact at 25-35 days after the EOT visit to collect data on concomitant medications, SAEs, and other safety events of interest. The overall duration of subject participation from screening through follow-up is therefore approx. 4½-5 months.

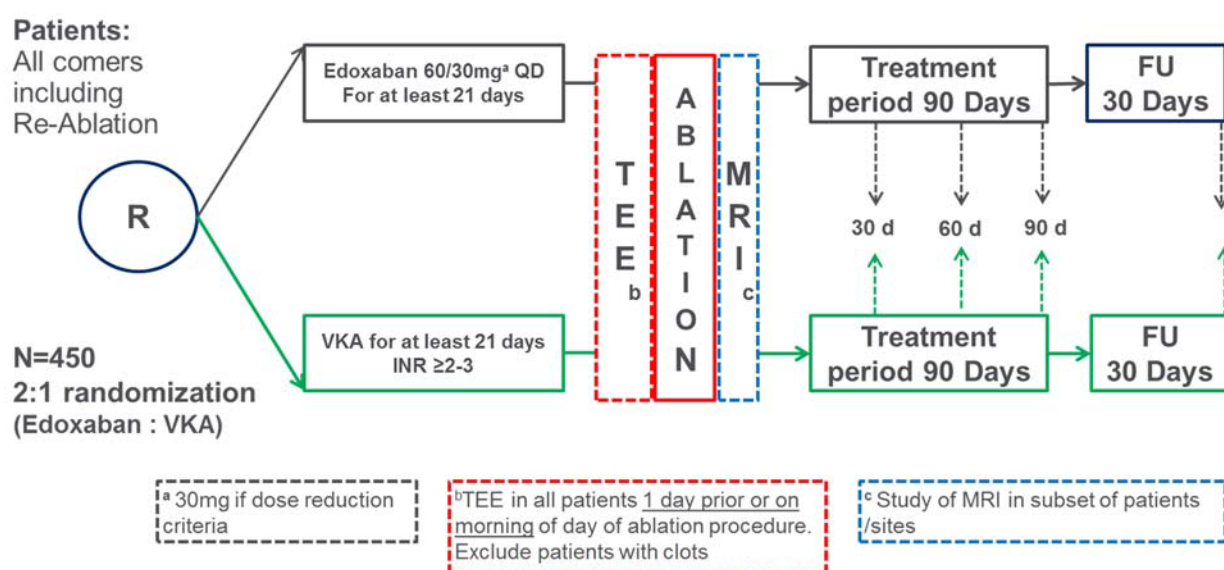
A schematic presentation of the study design is provided in Figure 3.1.

At Day 90, the subject will either discontinue the treatment completely or will be transitioned to an available marketed OAC of the Investigator's choice. The Investigator will follow the transition strategy in the approved product label.

All information must be captured in the electronic case report form (eCRF) and study assessments are performed according to the visit schedule provided under Section 16.9. Subjects who prematurely discontinue study OAC are requested to continue clinical follow-up with study visits according to this schedule.

The study organization, including the Clinical Events Committee (CEC), Data and Safety Monitoring Board (DSMB), Executive Committee and Steering Committee are described in appendix Section 16.1. An independent DSMB reviews pertinent study data to protect the safety of the subjects participating in the study.

Figure 3.1 Study Design



Note: For patients to undergo ablation, INR was to be between 2.0 to 3.0. If INR was ≥ 1.5 and < 2.0 or > 3.0 and ≤ 3.5 , ablation could be performed at the Investigator's discretion only

3.2. Discussion of Study Design

This study is designed to evaluate descriptively the safety and to explore the efficacy of an edoxaban-based antithrombotic regimen versus a VKA-based antithrombotic regimen in subjects undergoing catheter ablation of non-valvular AF. A parallel group design with VKA serving as the control arm has been selected to provide comparative data.

The duration of anticoagulant treatment prior to catheter ablation of 21 (up to +7) days is in accordance with the European Heart Rhythm Association (EHRA) position paper (17), which states ‘All patients undergoing AF ablation who present in AF for the procedure should be anticoagulated for at least 3 weeks prior to AF ablation. If they have not been anticoagulated prior to ablation, a TEE should be performed. In addition to adhering to these well-established anticoagulation guidelines that apply to cardioversion, the 2012 HRS/EHRA/ECAS consensus document recommends that all patients being anticoagulated during AF ablation with heparin to achieve an activated clotting time (ACT) of at least 300 s. This writing group fully supports these prior minimum recommendations for anticoagulation.’ Likewise, the requirement for patients treated with a VKA or a NOAC to have at least 3 weeks of effective stable INR at therapeutic levels (between 2 and 3 for VKA) is also in-line with these recommendations. The treatment duration after the ablation procedure is in-line with the recent ESC guidelines that recommend that anticoagulation should be maintained for at least 8 weeks after ablation for all patients (2).

This study requires TEE or alternatively intracardiac echocardiogram in all patients to ensure appropriate anticoagulation in the 3 weeks before the intervention in both arms.

The endpoints selected are relevant for the study. Bleeding is a central safety outcome in cardiovascular clinical trials, especially for antithrombotic strategies and invasive procedures (18, 19, 20).

4. STUDY POPULATION

4.1. Enrollment

Investigators will maintain a confidential pre-screening log of all potential study candidates that includes limited information of the subjects (age, sex), date and outcome of screening process (e.g., enroll in the study, reason for not participating).

Investigators will be expected to maintain an Enrollment Log of all subjects enrolled in the study indicating their assigned study number.

Investigators will maintain a confidential subject identification (ID) code list. This confidential list of names of all subjects allocated to study numbers on enrolling in the study, allows the Investigator to reveal the identity of any subject when necessary.

A subject is considered to be enrolled after the ICF has been signed. A unique study ID number is provided through the interactive web/voice response system (IXRS) together with the randomized treatment assignment.

4.1.1. Inclusion Criteria

Subjects must satisfy all of the following criteria to be included in the study:

1. Male or female at least 18 years of age with documented history of paroxysmal (lasting ≤ 7 days), persistent (lasting > 7 days but ≤ 12 months) or long-standing [long-lasting] persistent (> 12 months) non-valvular AF. Duration of AF can be confirmed by any electrical tracing or a recording in the subject's medical records (e.g., medical chart, hospital discharge summary).
2. Subject is eligible and is scheduled for either radiofrequency (RF) or cryoballoon catheter ablation (both first and repeated procedure included).
3. Signed ICF.

4.1.2. Exclusion Criteria

Subjects who meet any of the following criteria will be disqualified from entering the study:

1. AF considered to be of a transient or reversible nature (such as in myocarditis, post-surgery, ionic disturbances, thyrotoxicosis, pneumonia, severe anemia etc.).
2. Subject post stroke, or with a systemic thromboembolic event within the past 6 months prior to randomization.
3. Subject has a thrombus in the left atrial appendage (LAA), left atrium (LA), left ventricle (LV), or aorta, or an intracardial mass.
4. Subject had a myocardial infarction (MI) within the 2 months prior to randomization or coronary artery bypass graft (CABG) surgery within 3 months prior to the randomization.
5. Subject has signs of bleeding, history of clinically-relevant bleeding according to ISTH, or conditions associated with high risk of bleeding such as past history of intracranial (spontaneous or traumatic), or spontaneous intraocular, spinal, retroperitoneal, or intra-

- articular bleeding; overt gastrointestinal (GI) bleeding or active ulcer within the previous year; recent severe trauma, major surgery, or deep organ biopsy; active infective endocarditis; uncontrolled hypertension (blood pressure [BP] above 170/100 mmHg); or hemorrhagic disorder including known or suspected hereditary or acquired bleeding or coagulation disorder in the last 12 months prior to randomization.
6. Subjects with mechanical heart valves, subjects with moderate to severe mitral stenosis and subjects who have new implantation (within 3 months prior to randomization) of a bioprosthetic heart valve, with or without AF.
 7. Subjects with a history of LAA occlusion/exclusion (either by surgery or by a procedure).
 8. Subjects with any contraindication for edoxaban, VKA, low molecular weight heparin (LMWH), heparin therapy including known allergies, hypersensitivity, or intolerance to any component of these drugs or its excipients.
 9. Subjects receiving dual antiplatelet therapy (DAPT, i.e., aspirin and P2Y₁₂ antagonist) or planned to receive DAPT during the study
 10. Unfractionated heparin (UFH), low molecular weight heparins (LMWH; enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), and oral anticoagulants (warfarin, dabigatran etexilate, rivaroxaban, apixaban etc.) cannot be used concomitantly to study medication. Any bridging with LMWH around the CA procedure is prohibited. During the CA procedure, UFH will be used according to standard of care to achieve ACT of 300 to 400 sec. Subjects who require chronic use of medicines affecting hemostasis such as higher doses of aspirin (acetylsalicylic acid [ASA]) (ASA up to 100 mg per day allowed) or chronic oral or parenteral intake of non-aspirin non-steroidal anti-inflammatory drugs (NSAID) on ≥ 4 days/week (use of NSAIDs via other routes is not restricted)
 11. Subjects with active liver disease or persistent (confirmed by repeat assessments at least a week apart) elevation of liver enzymes/bilirubin:
 - Alanine transaminase (ALT) or aspartate transaminase (AST) ≥ 2 times the upper limit of normal (ULN)
 - Total bilirubin (TBL) ≥ 1.5 times the ULN (subjects whose elevated TBL is due to known Gilbert's syndrome may be included in the study)
 - Hepatic disease associated with coagulopathy and clinically relevant bleeding risk.
 12. Subjects with kidney failure (calculated creatinine clearance [CrCL] < 15 mL/min).
 13. Subjects with hemoglobin < 10 g/dL or platelet count $< 100,000$ cells/ μ L or white blood cell (WBC) count < 3000 cells/ μ L.
 14. Subjects with pre-planned invasive diagnostic or therapeutic procedures/interventions (other than endoscopy) during the study period in which bleeding is anticipated.
 15. Participation in any other interventional trial (subjects who received any investigational drug or device within 30 days prior to randomization, or plan to receive such investigational therapy during the study period).

16. Previous randomization in this study.
17. Female subjects of childbearing potential without using highly effective contraception (female of childbearing potential is defined as one who has not been postmenopausal for at least one year, or has not been surgically sterilised, or has not had a hysterectomy at least three months prior to the start of this study). Females taking oral contraceptives should have been on therapy for at least three months. Adequate contraceptives include: Combined (estrogen and progestogen containing) oral, intravaginal or transdermal hormonal contraception associated with inhibition of ovulation; progestogen-only oral, injectable or implantable hormonal contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomized partner; sexual abstinence.
18. Pregnant or breast-feeding subjects.
19. Subjects with the following diagnoses or situations:
 - Active cancer undergoing chemotherapy, radiation or major surgery within the next 5 months
 - Significant active/uncontrolled concurrent medical illness
 - Life expectancy <6 months.
20. Subjects who are unlikely to comply with the protocol (e.g., uncooperative attitude, inability to return for subsequent visits, and/or otherwise considered by the Investigator to be unlikely to complete the study).
21. Subjects with a known drug or alcohol dependence within the past 12 months prior to randomization as judged by the Investigator.
22. Subjects with any condition that, in the opinion of the Investigator, would place the subject at increased risk of harm if he/she participated in the study.
23. Planned procedure using laser catheter ablation or other forms of catheter ablation different from RF or cryoballoon (i.e. high intensity focused ultrasound [HIFU], microwaves, hot balloon, etc).

4.2. Screening Failures

Subjects are screened based on the information available from the standard care. For subjects fulfilling the eligibility criteria, signature of the ICF must take place before any study-specific screening procedures occur. A subject who withdraws IC before randomization or who fails the inclusion/exclusion criteria before randomization is defined as a screening failure. No further clinical follow-up is performed for these subjects.

If subjects fail the screening procedure, investigators can discuss with the medical monitor if they feel a subject might be suitable for rescreening.

5. STUDY TREATMENTS

5.1. Method of Assigning Subjects to Treatment Regimens

5.1.1. Treatment Groups

- Edoxaban 60 mg once-daily or 30 mg once-daily in selected subjects (see Section 5.2.1.2).
- Oral VKA, as pre-defined per country, with once-daily dosing for target INR between 2.0-3.0, inclusive.

The VKA pre-defined for the various countries are shown below:

Country	Pre-defined VKA
Belgium	Phenprocoumon & Warfarin
Canada	Warfarin
Czech Republic	Warfarin
France	Fluindione (Previscan®)
Germany	Phenprocoumon
Hungary	Warfarin
Italy	Warfarin
Korea	Warfarin
Netherlands	Phenprocoumon
Poland	Warfarin
Spain	Acenocoumarol (Sintrom®)
Taiwan	Warfarin
United Kingdom	Warfarin

5.1.2. Method of Treatment Allocation

After the IC has been signed and eligibility confirmed, the Investigator contacts the IXRS to register a new subject and assign an individual study ID number.

The Investigator should be prepared to provide subject information, including, but not limited to: date of IC, subject's year of birth, and gender.

Then the Investigator contacts IXRS to randomize subject into the study. The investigator should be prepared to confirm the subject's eligibility criteria and information about body weight, and CrCL using Cockcroft-Gault (in the course of the study, other formula will also be used, e.g., CKD-EPI Equation; see Section 16.6). Also the investigator will be asked to provide information whether the subject is taking concomitant P-gp inhibitors requiring edoxaban dose reduction (or other dose reduction relevant medication according to local labelling or IB, as applicable).

Subjects will be assigned randomly via the above mentioned IXRS such that the study has a 2:1 ratio of subjects in the edoxaban:VKA treatment arms.

The specifications for generation of the randomization schedule will be prepared by the study biostatistician and the IXRS vendor. An independent biostatistician, not otherwise part of the study team, will generate the randomization schedule. For this study, the randomization schedule refers to a list that includes at least the subject ID, randomization block number, and randomization treatment.

5.1.3. Blinding

This is an open-label study with blinded endpoint evaluation.

5.2. Study Drugs

5.2.1. Edoxaban

All dispensations must take place through the IXRS, which will provide the appropriate drug supply kit number.

5.2.1.1. Description

Edoxaban tosylate (DU-176b, trade names Lixiana®, Savaysa®), referred throughout this protocol by the term "edoxaban" for simplicity. Please refer to Section 5.3.

Importantly, it is mandatory in this study that in the pre-ablation period, the once-daily dose of edoxaban is taken every day in the evening. Patients will be instructed to swallow the tablet, preferably with water. Edoxaban can be taken with or without food (7).

If a dose of edoxaban is missed, the dose must be taken as soon as possible as long as on the same day. The dose of edoxaban must not be doubled to make up for a missed dose.

5.2.1.2. Dose

The dose of edoxaban is 60 mg once-daily but will be reduced to 30 mg once-daily, if the subject has one of the following:

- Moderate to severe renal impairment ($\text{CrCL} \geq 15$ to ≤ 50 mL/min as calculated using the Cockcroft-Gault formula)
- Low body weight (≤ 60 kg)

- Subjects being treated with P-gp inhibitors may require dose reduction, please refer to local label or IB.

Remark: In EU countries, according to the Summary of Product Characteristics (SmPC) concomitant use of edoxaban with cyclosporine, dronedarone, erythromycin, or ketoconazole requires dose reduction to 30 mg once-daily.

Concomitant use of edoxaban with quinidine, verapamil, or amiodarone does not require dose reduction.

All edoxaban dosage adjustments will be implemented through the IXRS. The IXRS will provide the appropriate drug supply kit number.

For low body weight (≤ 60 kg) present at randomization, the edoxaban dose is reduced permanently and even if the subject gains weight, the edoxaban dose remains reduced. Otherwise, the dose of edoxaban returns to the regular dosage regimen of 60 mg once-daily any time the subject no longer displays any of the other above mentioned factors.

After randomization and in subjects without dose reduction, if a subject's:

- body weight drops to ≤ 60 kg, then the edoxaban dose is reduced (i.e., to 30 mg once-daily) permanently.
- CrCL becomes ≤ 50 mL/min, then the edoxaban dose is reduced to 30 mg once-daily.
- Or if a subject develops the need for concomitant treatment with the P-gp inhibitors cyclosporine, dronedarone, erythromycin, or ketoconazole which require edoxaban dose adjustment, then the edoxaban dose is reduced (i.e., to 30 mg once-daily).

Remark: In EU countries, according to SmPC concomitant use of edoxaban with cyclosporine, dronedarone, erythromycin, or ketoconazole requires dose reduction to 30 mg once-daily. Concomitant use of edoxaban with quinidine, verapamil, or amiodarone does not require dose reduction.

The dose of 15 mg edoxaban once-daily is not indicated as monotherapy and is solely provided as part of transitioning from edoxaban 30 mg at the end of study (see Section 5.2.1.4).

5.2.1.3. Transitioning to Edoxaban at Randomization

For subjects randomized to the edoxaban-based regimen that require switching from another anticoagulant the following algorithm should be used (Table 2).

Table 2: Transitioning to Edoxaban at Randomization

Switching to edoxaban		
From	To	Recommendation
VKA	Edoxaban	Discontinue the VKA and start edoxaban when INR is ≤ 2.5 .
Other non-VKA OAC drugs <ul style="list-style-type: none"> • dabigatran • rivaroxaban • apixaban 	Edoxaban	Discontinue the OAC and start edoxaban at the time of the next OAC dose.

INR = International Normalized Ratio; OAC = oral anticoagulant; VKA = vitamin K antagonist

5.2.1.4. Transition from Edoxaban at End of Treatment

For subjects randomized to the edoxaban-based regimen that require switching from edoxaban to another anticoagulant at the scheduled EOT (or due to a premature edoxaban discontinuation) the following algorithm should be used (Table 3).

Table 3: Transitioning from Edoxaban at End of Treatment

Switching from edoxaban		
From	To	Recommendation
Edoxaban	VKA	<p>During the transition from edoxaban to VKA continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant.</p> <p>Oral option:</p> <ul style="list-style-type: none"> For subjects currently on a 60 mg once-daily dose, administer an edoxaban dose of 30 mg once-daily together with an appropriate VKA dose. For subjects currently on a 30 mg dose once-daily (for one or more of the following factors: moderate to severe renal impairment (CrCL 15-50 mL/min), low body weight, or use with certain P-gp inhibitors), administer an edoxaban dose of 15 mg once-daily together with an appropriate VKA dose. Edoxaban 15 mg once-daily is not indicated as monotherapy, as it may result in decreased efficacy. It is only indicated in the process of switching from edoxaban 30 mg once-daily to VKA, together with an appropriate VKA dose. <p>Subjects should not take a loading dose of VKA in order to promptly achieve a stable INR between 2.0 and 3.0. It is recommended to take into account the maintenance dose of VKA if the patient was previously taking a VKA or to use valid INR driven VKA treatment algorithm, in accordance with local practice. Once an INR ≥ 2.0 is achieved, edoxaban should be discontinued. Most patients (85%) should be able to achieve an INR ≥ 2.0 within 14 days of concomitant administration of edoxaban and VKA. After 14 days it is recommended that edoxaban is discontinued and the VKA continued to be titrated to achieve an INR between 2.0-3.0. It is recommended that during the first 14 days of concomitant therapy the INR is measured at least three times just prior to taking the daily dose of edoxaban to minimize the influence of edoxaban on INR measurements. Concomitant edoxaban and VKA can increase the INR post edoxaban dose by up to 46%.</p>
		<p>Parenteral option:</p> <p>Discontinue edoxaban and administer a parenteral anticoagulant and VKA at the time of the next scheduled edoxaban dose. Once a stable INR of ≥ 2.0 is achieved, the parenteral anticoagulant should be discontinued and the VKA continued.</p>
Edoxaban	Other non-VKA OAC drugs	Discontinue edoxaban and start the non-VKA anticoagulant at the time of the next scheduled dose of edoxaban.
Edoxaban	Parenteral anticoagulants	These agents should not be administered simultaneously. Discontinue edoxaban and start the parenteral anticoagulant at the time of the next scheduled dose of edoxaban.

CrCL = creatinine clearance; INR = International Normalized Ratio; OAC = oral anticoagulant; P-gp = P-glycoprotein; VKA = vitamin K antagonist

5.2.2. Vitamin K Antagonist

All VKA must be dispensed via the IXRS that will provide the appropriate drug supply kit number.

5.2.2.1. Dose

The Investigator monitors the INR and adjusts the VKA dose to maintain the INR within target. It is the Investigator's responsibility to collect INR assessments and record these throughout the study. A preferred VKA is selected for each participating country (for more details, please refer to Section 5.1.1) which is provided as study medication:

- **Warfarin**
Loading dose from 2-5 mg once-daily for 2-4 days followed by a maintenance dose of 2-10 mg once-daily adjusted by INR values to maintain target INR between 2.0-3.0 inclusive.
- **Phenprocoumon**
Weekly dose calculation of up to 9 mg on Day 1, 6 mg on Day 2 and maintenance doses between 1.5-6.0 mg once-daily thereafter, adjusted by INR values to maintain target INR between 2.0-3.0 inclusive.
- **Fluindione**
The initial daily dose of 20 mg is adjusted by INR values to maintain target INR between 2.0-3.0 inclusive. In subjects at particular risk of bleeding (weight <50 kg, elderly, hepatic impairment), the initial dose is usually lower. No loading dose should be used. The dose adjustment is performed in accordance to the package insert and usually by increments of 5 mg (1/4 tablet).
- **Acenocoumarol**
The usual starting dose in a normal weight person is between 2-4 mg/day without administration of a loading dose, if the INR value before the start of treatment is within the normal range. Treatment may also be initiated with a loading dose regimen, usually 6 mg on the first day followed by 4 mg on the second day. The maintenance dose generally lies between 1-8 mg once-daily, adjusted by INR values to maintain target INR between 2.0-3.0 inclusive.

The dosing of the aforementioned VKAs must be individualized. The maintenance dose varies from subject to subject and its appropriateness must be checked individually on basis of INR values.

Subjects will take the VKA according to the direction of the Investigator.

The Investigator or designee is responsible for dispensing the VKA antagonist and must ensure that drug supplied by Sponsor is used in accordance with the protocol and the VKA package insert.

5.2.2.2. Transitioning to Study Vitamin K Antagonist at Randomization

Subjects are transitioned to an available study VKA (country specific as provided by IXRS, see Section 5.1.1. for details). The Investigator will follow the transition strategy in the approved product label.

For subjects not previously on VKA, commonly initial doses of VKA are higher than the maintenance doses which will be used after the INR is stabilized. For these subjects bridging with parenteral anticoagulation is permissible. For initiation of VKA therapy and related bridging with parenteral anticoagulation, follow locally established guidelines and local approved label (prescribing information) from the VKA manufacturer.

For subjects randomized to VKA: If subject is on:

- VKA, continue with study VKA when INR ≤ 2.5 .
- NOAC, discontinue the NOAC and start study VKA at the time of the next scheduled NOAC dose.

For subjects randomized to VKA who require switching from another anticoagulant (another VKA, other non-VKA OAC drugs or parenteral anticoagulants), follow the guidance for switching in the locally approved labels of these products. Capture the date and timing of first study dose in eCRF.

5.2.2.3. International Normalized Ratio Management

Every attempt will be made to bring subjects into the therapeutic target range (INR 2.0-3.0) as fast as possible and to maintain the target INR range consistently. Close attention to the INR management plan and frequent monitoring of INR values is strongly recommended to optimize the VKA treatment and maintain the subject's INR values between 2.0-3.0 inclusive. The Investigator will ensure the VKA is used according to the approved label (prescribing information).

Frequent INR determinations upon initiation should be obtained until subject's INR is stable in the therapeutic range. It is expected that more frequent visits will be planned for 'de novo' subjects on VKA to adjust the dose with the goal of reaching INR 2.0-3.0 within 6-8 days after enrolment. Obtain subsequent INR determinations as per recommendations and guidelines provided in the local approved label from the respective VKA manufacturer.

Before ablation, each subject must be in the INR range of 2.0-3.0 for the last 10 days prior to the catheter ablation. This will need to be documented by frequent INR measurements, at least once per week in the pre-ablation period. On the day of, or the day prior to, the scheduled ablation procedure, subjects INR should be within the range 2.0-3.0. If INR is ≥ 1.5 and < 2.0 or if INR is > 3.0 and ≤ 3.5 the procedure may be performed at the Investigator's discretion.

After ablation, when the subjects' anticoagulation is more constant, the frequency of INR measurements may be lower than in the pre-ablation period. However, in the post-ablation period, at least monthly INR controls are required.

INR values and VKA dose are collected either during the on-site visits or by local laboratory determination. INR values and VKA doses collected through the general practitioner or local anticoagulation clinic must also be considered and collected but this does not constitute a waiver for subjects' planned INR determination during on-site visits. In any case the study physician is

responsible for checking the INR value, adapting the VKA dose accordingly, and for entering all the data into the eCRF.

5.2.2.4. Transition from Vitamin K Antagonist at End of Treatment

Subjects are transitioned to an available marketed OAC of the Investigator's choice. The Investigator will follow the transition strategy in the approved product label. Subjects who prematurely discontinue study OAC are requested to continue clinical follow-up with study visits according to this schedule.

5.2.3. Interruptions and Discontinuations of Study Treatment

The intended duration of the two study treatments after ablation is 90 days. Subjects stay on the assigned regimen as much as possible.

Permanent discontinuation of the assigned regimen is mandatory if the CrCL falls below 15 mL/min on two consecutive occasions or if subject is placed on dialysis. If the Investigator doubts the accuracy of the CrCL value calculated with the Cockcroft-Gault formula, he/she may consider calculating CrCL using a 24-hour urine collection, for confirmatory purposes. If a subject's CrCL, calculated with either the Cockcroft-Gault formula or 24-hour urine collection, recovers to ≥ 15 mL/min, the subject should resume study regimen in line with the applicable labels.

For subjects with a suspected transient decrease in CrCL < 15 mL/min it is recommended that repeat testing of CrCL occur after corrective action is taken or when the medical condition that caused the worsening renal function resolves. The timing of the repeat testing is at the discretion of the Investigator and will vary depending on the nature of the medical condition (e.g., 1-2 weeks for urinary tract infection or over diuresis vs. several weeks to months for glomerulonephritis).

If other clinical contraindications for any study medication develop (according to the label of the respective drug), the study medication must be discontinued (or dose decreased if applicable). If the contraindication resolves, the respective study medication is restarted. During each interruption of anticoagulant therapy, subjects are evaluated to determine whether the subject can safely resume the study drug. A post-randomization change in health status that results in the subject meeting one or more of the exclusion criteria should only lead to interruption or discontinuation of the assigned medications if the change in health status implies a contraindication according to the drug labels.

Study medications are permanently discontinued if the subject refuses continuation of any medication in the assigned study regimens.

All study medication start and stop dates are captured in eCRF together with the reason for interruption or discontinuation.

5.3. Labeling and Packaging

The Investigators/study coordinators must ensure that the appropriate fields on the label are completed, including unique subject ID and initials.

The Investigator provides the subjects with sufficient study medications to last until the next scheduled dispensing visit.

Edoxaban is supplied as 30 or 60 mg film coated tablets (30 mg or 15 mg as transition medication if applicable) for oral use and will be provided to all sites via IXRS. Materials are supplied and labelled with a single panel multilingual booklet.

VKA medication for oral use and will be provided to all sites via IXRS. Materials are supplied and labelled with a single panel multilingual booklet. The Sponsor will provide an oral preferred VKA as pre-selected by country, being either:

- **Warfarin** supplied as commercially available tablets of 1 mg, and 2.5 mg in wallets with blisters.
- **Phenprocoumon** supplied as commercially available tablets of 3 mg strength in wallets with blisters.
- **Fluindione** supplied as commercially available tablets of 20 mg strength in wallets with blisters. Fluindione supply is exclusive to France and will not be available in other participating countries. Fluindione is only labelled in French.
- **Acenocoumarol** supplied as commercially available tablets of 4 mg strength in wallets with blisters.

5.4. Preparation

All investigational products will be supplied as tablets that need no further preparation at the sites.

5.5. Administration

Edoxaban will be administered in accordance with the local label or IB, and VKA will be administered in accordance with the approved local label.

5.6. Storage

When a drug shipment is received, the Investigator or designee will do the following within 48 hours of receipt: check the amount and condition of the drug, check for appropriate local language on the label, check the drug expiration date, and sign the Receipt of Shipment Form provided. The site will acknowledge receipt of the shipment in the IXRS. All instructions on the Receipt of Shipment Form will be followed, and the form will be filled in at the site. In addition, the Investigator or designee will contact the site monitor as soon as possible but within 48 hours, if there is a problem with the shipment.

Drug supplies must be stored in a secure, limited access storage area under the recommended storage conditions as measured by a minimum/maximum thermometer. Temperature measurement will be recorded daily on a temperature log, excluding weekends and holidays. The sponsor and site monitor must be contacted in the event of a temperature excursion outside of the recommended storage conditions.

5.7. Drug Accountability

The eCRF contains a drug accountability module for medications supplied by the sponsor. The Investigator or designee enters the required information in this module.

At the end of the study, or as directed, all medications supplied by the sponsor, including unused, partially used, or empty containers, will be returned to a designee as instructed by Daiichi Sankyo Europe (DSE) or destroyed at the site. Investigational Product will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return of all study medications must be documented and the documentation included in the shipment. At the end of the study, a final study medication reconciliation statement must be completed by the Investigator or designee and provided to the sponsor. Drug supplies may be destroyed by the Investigator when approved in writing by DSE and DSE has received copies of the site's drug handling and disposition standard operating procedures (SOPs).

All inventory forms must be made available for audits by a sponsor authorized representative or designee and /or inspections by regulatory agency inspectors. The Investigator is responsible for the accountability of all used and unused medications provided by the sponsor at the site.

5.8. Method of Assessing Regimen Compliance

Each subject should document missed doses in the subject booklet. The subject should be instructed by the Investigator to bring this booklet to any visit so that the relevant information can be captured in the eCRF.

At each visit, the Investigator or designee assesses the subject's compliance with the assigned regimen by asking the subject about missed doses and visually inspecting the drug supply the subject brought to the visit. The Investigator or designee assesses the compliance of edoxaban, by tablet counts, and captures information in the eCRF. If zero tablets are returned while an overage is expected, the subject should be asked whether any were disposed/thrown away, rather than taken orally.

Moreover, the Investigator captures the exposure to edoxaban and VKA in the eCRF:

- The information provided by the subject on their medication log.
- Information provided by subject during site visits or site telephone assessments concerning missed doses (date, drug and reason).
- For VKA, the Investigator assesses the INR at local laboratory at each on site visit and uses the determined INR value in the assessment of VKA exposure and target INR between 2.0-3.0. It is the Investigator's responsibility:
 - o to monitor the INR and adjust the VKA dose to maintain the INR within target, and
 - o to collect at least monthly INR assessments and record these throughout the study.
- In case of a suspected study endpoint, an additional assessment for subject compliance to the assigned regimen must be performed.

5.9. Prior and Concomitant Medications

Prior medications that the subject has taken within 30 days before randomization are recorded in the eCRF. These medications taken by the subjects prior to randomization or at any time during the study are regarded as concomitant medications and must be documented on the appropriate pages of the eCRF.

If the subject experiences a study endpoint event (see Section 7.1 and 7.3, including individual components) or an SAE, then information on concomitant medications taken within the past 30 days must be documented in the appropriate eCRF pages.

Concomitant medication use is captured in the eCRF until the post-treatment follow-up visit.

Medications listed below are allowed with the following restrictions:

- ASA is allowed if dose \leq 100 mg once-daily
- In the edoxaban-based regimen, edoxaban dose reduction to 30 mg once-daily is required during concomitant use with the P-gp inhibitors cyclosporine, dronedarone, erythromycin, or ketoconazole (please refer to local labelling or to the IB, as applicable); Remark: In EU countries, according to the SmPC concomitant use of edoxaban with cyclosporine, dronedarone, erythromycin, or ketoconazole requires dose reduction to 30 mg once-daily. Concomitant use of edoxaban with quinidine, verapamil, or amiodarone does not require dose reduction.

5.9.1. Prohibited Medications

The following drugs **are not permitted** during the treatment period:

- Additional anticoagulants, other than the assigned edoxaban or VKA, by any route (with the exception of parenteral agents used to treat a new clinical event, such as acute coronary syndrome, or as a bridge when starting or resuming the assigned VKA);
- Dual antiplatelet therapy (DAPT, i.e., aspirin and P2Y₁₂ antagonist);
- Fibrinolytic agents, unless required to treat a new clinical event, such as acute MI, PE, or stroke, in which case the risks and benefits of such treatment should be considered and, if given, the assigned edoxaban or VKA should be temporarily discontinued;
- Chronic use of medicines affecting hemostasis such as higher doses of ASA (ASA up to 100 mg per day allowed) or chronic oral or parenteral intake of non-aspirin NSAIDs on \geq 4 days/week (use of NSAIDs via other routes is not restricted);
- Vitamin K substitution medications;
- Investigational drugs (other than the randomized study treatment regimen).

Subjects on these drugs at the time of randomization cannot be included into the study. After randomization, short-term concomitant use of these drugs may require a study medication interruption. All study medication interruptions must be captured in the eCRF. After completion of a short course of therapy with the prohibited drug, the interrupted study medication may be resumed. Longer-term concomitant use of these drugs (e.g., new indication for chronic DAPT) will require withdrawal of the subject from the study.

5.10. Subject Withdrawal/Discontinuation

In accordance with the Declaration of Helsinki and other applicable regulations, a subject has the right to withdraw consent for participation in the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

5.10.1. Reasons for Withdrawal

Any subject who is withdrawn from the study treatment for any reason will have their reasons for withdrawal recorded. Subjects may be withdrawn from the study after signing the ICF for the following reasons:

- AE
- Withdrawal by subject
- Physician decision
- Death
- Lack of efficacy
- Pregnancy
- Protocol deviation
- Study terminated by sponsor
- Lost to follow-up
- Other

5.10.2. Withdrawal Procedures

If a subject is withdrawn from the study, the Investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal including the date of last treatment and the reason for withdrawal.

If the subject is withdrawn due to an AE, the Investigator will follow the subject until the AE has resolved or stabilized.

All subjects who are withdrawn from the study should complete protocol-specified withdrawal procedures. Subjects will be followed in the trial (for all protocol specified evaluations of efficacy or safety events, concomitant therapies, etc) unless there is written documentation of withdrawn consent (by the subject and/or by the Investigator).

6. STUDY PROCEDURES

A tabular summary of the visit schedule for the study is provided in Section 16.9. The medications used in the study regimens are provided by the Sponsor and details on drug accountability are provided in Section 5.7.

Subjects eligible to participate in the study must have signed the ICF before randomization or any study-specific procedures are performed. After the ICF is signed, subjects are randomized without delay to one of the two study arms (2:1 edoxaban vs. VKA).

6.1. Pre-screening

The pre-screening will be done outside the protocol at the site's discretion though information required by the protocol will need to be recorded in the eCRF and subject notes.

6.2. Subject Enrollment (Screening/Randomization, Visit 1, Day -21 (max. Day -28) and Optional Visit 2 Day -14)

The screening period will be 1-3 days. Visits for Screening and Randomization may be combined if the Inclusion/Exclusion criteria can be checked on the basis of the patient's health record and actual laboratory results with sufficient accuracy and if the subject has been handed out the ICF at least 1 day before randomization and preconditioned that all of the subject's questions could be answered.

Enrollment of subjects will occur between 21 to 28 days before the procedure. Subjects will undergo study specific procedures only after the ICF is signed. This visit may be split into two steps at baseline as per local requirements. In the pre-ablation treatment period, an optional visit may occur for those patients who do not have the option of INR measurement in an ambulatory setting (optional Visit 2, Day -14).

The following activities and/or assessments are performed prior to randomization and the outcomes recorded in the eCRF:

- ICF signed;
- Check that the subject meets all of the inclusion criteria and none of the exclusion criteria (see Section 4.1); in case that Randomization is not at the same day as Screening, inclusion and exclusion criteria will be re-assessed at Randomization;
- Collect demography information (age, body weight and gender)
- Review medical history including bleeding history and history of cardioversions;
- Record prior medication within the 30 days prior to randomization;
- Physical examination;
- Blood draw for central lab at Screening:
 - Creatinine, estimated CrCL according to the Cockcroft-Gault formula (see Section 16.6),

- Red Blood Cell count and status (e.g., hemoglobin, hematocrit), platelet count, WBC (with differential if elevated), TBL (if elevated, determine conjugated/unconjugated bilirubin fraction), ALT, AST, alkaline phosphatase, INR in all subjects;
- Total cholesterol and triglycerides only done at screening;
- Blood draw for central laboratory analysis of cardiac markers.

If available recent local laboratory results are of sufficient accuracy to verify the patient's eligibility and support randomization in the judgment of the investigator the patient can be randomized on the same day as screening.

- Women of childbearing potential must have a negative urine test for pregnancy at screening (a female of childbearing potential is defined as one who has not been postmenopausal for at least one year, or has not been surgically sterilised, or has not had a hysterectomy at least 3 months prior to the start of this study). These subjects must be willing and able to use adequate contraception and adhere to the following prohibitions and restrictions: Females taking oral contraceptives should have been on therapy for at least three months. Adequate contraceptives include: Combined (estrogen and progestogen containing) oral, intravaginal or transdermal hormonal contraception associated with inhibition of ovulation; progestogen-only oral, injectable or implantable hormonal contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomized partner; sexual abstinence. This test will be confirmed at Visit 3 (Baseline / Day 0 / catheter ablation day) and Visit 6 (Site Visit Day 30). Furthermore, pregnancy tests are carried out whenever there are clinical indications for the existence of a pregnancy.

Eligible subjects should be randomized without delay. The Investigator will contact the IXRS and provide the following information:

- Confirmation that ICF has been signed and dated;
- Demography (year of birth, body weight and gender);
- Confirm if CrCL is less or equal 50 mL/min. or >50 mL/min.;
- Usage of a P-gp inhibitor that requires an edoxaban dose reduction (according to local edoxaban labelling or IB as applicable);
- Confirmation subject fulfills all inclusion and none of the exclusion criteria.

Subject ID number will be assigned through IXRS and the following if the subject is randomized:

- the randomized treatment regimen;
- presence of edoxaban dose reduction requirement;
- kit numbers of the medications to be used.

After randomization,

- The assigned study medication and the proper daily dosing is explained to the subject. It is also explained how the drug accountability is documented in the study.

For subjects randomized to edoxaban (see Section 5.2.1. for more details): If subject is on:

- (a) VKA, discontinue the VKA and start edoxaban when INR is ≤ 2.5 .
- (b) NOAC, discontinue NOAC and start edoxaban at the time of the next scheduled NOAC dose.

In the pre-ablation period, it is mandatory that the once-daily dose of edoxaban is taken in the evening.

For subjects randomized to VKA (see Section 5.2.2. for more details): If subject is on:

- (a) VKA, continue with medication as provided by IXRS when INR ≤ 2.5 .
- (b) NOAC, discontinue the NOAC and start VKA at the time of the next scheduled NOAC dose.

- Instruction is provided to the subject to bring all study medication to each visit, including edoxaban. Each subject should document missed doses in the subject booklet. The subject should be instructed by the Investigator to bring this booklet to any visit so that the relevant information can be captured and Investigator captures information in the eCRF.
- Only for VKA subjects: obtain INR and VKA dose information. Frequent INR determinations upon initiation should be obtained until subject's INR is stable in the therapeutic range. It is expected that more frequent visits will be planned for 'de novo' subjects on VKA to adjust the dose with the goal of reaching INR 2.0-3.0 within 6-8 days after enrolment. Obtain subsequent INR determinations as per recommendations and guidelines provided in the local approved label from the respective VKA manufacturer.
- Vital signs (heart rate, sitting blood pressure, height [at randomization only], and body weight);
- 12-lead ECG;
- Concomitant medication;
- AE and suspected clinical events reporting.

The Sponsor will supply study subjects with edoxaban and VKA for the pre-ablation study period according to assigned regimen at randomization. Medication kits are assigned through the IXRS. Accountability for medications provided by DSE is performed at dispensing visits and the EOT visit.

All subjects will be required to complete at least 21 (up to +7) days of anticoagulation prior to the cardiac ablation.

6.2.1. Edoxaban Study Arm

Subjects receiving anticoagulants at the time of enrollment will be switched to edoxaban (the switching procedure will follow the edoxaban label and is described in Section 5.2.1.3). It is

mandatory that in the pre-ablation period, the once-daily dose of edoxaban is taken in the evening.

6.2.2. VKA Study Arm

Subjects enrolled in the VKA study arm will be required to complete at least 21 days (+7 days) of anticoagulation treatment with VKA. Subjects will take the VKA according to the direction of the Investigator. Every attempt will be made to bring subjects into the therapeutic target range (INR 2.0-3.0) as fast as possible and to maintain the target INR range consistently.

INR will need to be measured frequently at the start of the study (unless a subject is receiving an unvarying VKA dose at the time of randomization) to record the time when INR reaches a level of ≥ 2.0 .

Before ablation, each subject must be in the INR range of 2.0-3.0 for the last 10 days prior to the catheter ablation. This will need to be documented by frequent INR measurements, at least once per week in the pre-ablation period. INR must be measured on the day of or the day prior to the scheduled ablation procedure. If INR is ≥ 1.5 and < 2.0 or if INR is > 3.0 and ≤ 3.5 on the day of or the day prior to the scheduled ablation procedure, the procedure may be performed at the Investigator's discretion. Otherwise, the subject is not eligible for performing the catheter ablation (the subject will be switched from study medication to standard of care and will enter the 30-day follow-up period).

During the catheter ablation procedure, VKA will be used without interruption and bridging with LMWH will not be allowed at this time.

6.3. Catheter Ablation Visit (Periprocedural Visit, Visit 3, Day 0)

The following activities and/or assessments are performed and the outcomes recorded in the eCRF:

- Administer and dispense study medication; the Sponsor will supply study subjects with edoxaban and VKA for the post-ablation study period;
- Subjects randomized to edoxaban will take edoxaban in the evening of the day before the ablation procedure. The interval between the last intake of edoxaban and the procedure must not exceed 18 hours. After the ablation, study medication must be re-started on the day of procedure but no earlier than 6 hours post-sheath removal and only after adequate hemostasis has been achieved.
- Obtain INR and VKA dose information (VKA subjects only);
- Vital signs (heart rate, blood pressure, body weight);
- 12-lead ECG recording;
- TEE or alternatively intracardiac echocardiogram - will be performed during the hospital stay related to the procedure directly before catheter ablation or the day before (up to 24 hours before ablation). If TEE or intracardiac echocardiogram is positive, i.e., shows clots, the cardiac ablation procedure will be canceled and the patient will be switched from study medication to standard of care and will enter a 30-day follow-up period;

- Catheter ablation procedure;
- Unfractionated heparin (UFH) administration/ ACT monitoring;
- Blood draw for central laboratory analysis including safety parameters (INR, liver function, serum chemistry, and hematology) as described in Section 9.7.
- Only in women of childbearing potential: urine test for pregnancy. Furthermore, pregnancy tests are carried out whenever there are clinical indications for the existence of a pregnancy;
- Concomitant medications;
- Review of treatment compliance and interruptions. Antithrombotic regimen compliance is achieved by assessing subject compliance (both by pill count, self-reporting/ physician-reporting and by INR values for VKA subjects only). In case of a suspected study endpoint, an additional assessment for subject compliance to the assigned regimen must be performed.
- (S)AEs and suspected clinical endpoints experienced by the subject since the last visit.
 - AEs (including abnormal laboratory findings and during unscheduled visits), endpoint events, and adverse events of special interest (AESI) should be reported as soon as site personnel learn of the event. Endpoint event and AE reporting should occur throughout the study and not be restricted to specific visits. If ALT or AST >3x ULN with simultaneous TBL >2x ULN is observed, then alkaline phosphatase (ALP) should be determined.

6.3.1. Edoxaban Study Arm

Subjects will be required to have completed at least 21 (up to +7) days of anticoagulation with edoxaban. It is mandatory that in the pre-ablation period, the once-daily dose of edoxaban is taken in the evening.

If a subject has taken the study drug in the evening and the TEE/intracardiac echocardiogram is negative, the procedure can be performed in the morning of the next day. The interval between the last intake of edoxaban and the procedure should not exceed 18 hours. After the ablation, study medication must be re-started on the day of procedure no earlier than 6 hours post-sheath removal and only once adequate hemostasis has been achieved.

Timing of the last dose of edoxaban prior to the catheter ablation procedure and the first dose after the procedure will be recorded in the eCRF.

6.3.2. VKA Study Arm

Before ablation, each subject must be in the INR range of 2.0-3.0 for the last 10 days prior to the catheter ablation. This will need to be documented by frequent INR measurements, at least once per week in the pre-ablation period. INR must be measured on the day of or the day prior to the scheduled ablation procedure. On the day of, or the day prior to, the scheduled ablation procedure, subjects INR should be within the range 2.0-3.0. If INR is ≥ 1.5 and < 2.0 or if INR is > 3.0 and ≤ 3.5 the procedure may be performed at the Investigator's discretion. Otherwise, the subject is

not eligible for performing the catheter ablation (the subject will be switched from study medication to standard of care and will enter the 30-day follow-up period).

During the catheter ablation procedure, VKA will be used without interruption and bridging with LMWH will not be allowed at this time.

6.3.3. Anticoagulation During Catheter Ablation

During ablation, heparin should be given to maintain an ACT >300 s (2). Heparin (standard of care treatment) should be administered (100 U/kg bolus) prior to or immediately following trans-septal puncture during AF ablation procedures and adjusted to achieve and maintain an ACT of 300 to 400 seconds. ACT levels should be checked at 15-20-minute intervals until therapeutic anticoagulation is achieved and then at 30-minute intervals for the duration of the procedure. Heparin anticoagulation will be partially reversed with protamine and sheaths removed at an ACT <250 seconds (15).

6.3.4. Anticoagulation Post Catheter Ablation

Following completion of the catheter ablation procedure, all subjects will continue receiving treatment within their study arm until Day 90 post-procedure. For patients randomized to edoxaban, after the ablation, study medication must be re-started on the day of procedure no earlier than 6 hours post-sheath removal and only once adequate hemostasis has been achieved. For subjects randomized to VKA when after ablation, the subjects' anticoagulation is more constant, the frequency of INR measurements may be lower than in the pre-ablation period. However, in the post-ablation period, at least monthly INR controls are required.

6.4. Hospital Discharge (Visit 4; optional)

This visit may be performed at the discretion of the Investigator. The following activities and/or assessments are performed at the hospital discharge visit and the outcomes recorded in the eCRF:

- Obtain INR and VKA dose information (VKA subjects only);
- Vital signs (heart rate, sitting blood pressure, body weight);
- 12-lead ECG recording;
- Concomitant medications (changes);
- (S)AEs and suspected clinical endpoints experienced by the subject since the last visit.

6.5. Diffusion-Weighted Magnetic Resonance Imaging (Selected sites only) (Visit 5, Day 4)

At selected sites, the following activities and/or assessments are performed and the outcomes recorded in the eCRF:

- Vital signs (heart rate, sitting blood pressure, body weight);
- DW-MRI or diffusion weighted imaging fluid attenuated inversion recovery (DWI-FLAIR) will be performed 4 days \pm 2 days post catheter ablation;
- (S)AEs and suspected clinical endpoints experienced by the subject since the last visit.

6.6. Site Visit (Visit 6, Day 30)

The following activities and/or assessments are performed and the outcomes recorded in the eCRF:

- Obtain INR and VKA dose information (VKA subjects only);
- Vital signs (heart rate, sitting blood pressure, body weight);
- 12-lead ECG recording;
- Blood draw for central laboratory analysis of safety parameters (INR, liver function, serum chemistry, and hematology); as described in Section 9.7.
- Only in women of childbearing potential: urine test for pregnancy. Furthermore, pregnancy tests are carried out whenever there are clinical indications for the existence of a pregnancy;
- Concomitant medications (changes);
- Review of treatment compliance and interruptions;
- (S)AEs and suspected clinical endpoints experienced by the subject since the last visit.

6.7. Optional Site Visit/Telephone Assessment (Visit 7, Day 60)

The following activities and/or assessments are performed and the outcomes recorded in the eCRF: A personal visit is optional for those patients who do not have the option of INR measurement by their general practitioner.

- Obtain INR and VKA dose information (VKA subjects only);
- Vital signs (heart rate, sitting blood pressure, body weight; only done if performed as personal visit);
- Concomitant medications (changes);
- Review of treatment compliance and interruptions.
- (S)AEs and suspected clinical endpoints experienced by the subject since the last visit.

6.8. End of Treatment (Visit 8, Day 90)

At Day 90, the subject will either discontinue the treatment completely or will be continued on any of the approved OAC drugs per physician's discretion. Detailed switching protocols according to medication label will be provided.

The EOT visit is performed for subjects who have a premature discontinuation of their assigned OAC-based regimen or who have modified their IC after randomization with full withdrawal of IC (see details Section 6.11). For these subjects, the scheduling of the EOT remains unchanged (i.e. 90 ± 5 days). In such cases, the EOT visit is the end-of-study visit/contact.

The following activities and/or assessments are performed and the outcomes recorded in the eCRF:

- Obtain INR and VKA dose information (VKA subjects only);

- Vital signs (heart rate, sitting blood pressure, body weight);
- 12-lead ECG recording;
- Blood draw for central laboratory analysis of safety parameters (INR, liver function, serum chemistry, and hematology) as described in Section 9.7;
- Concomitant medications (changes);
- Review of treatment compliance and interruptions;
- (S)AEs and suspected clinical endpoints experienced by the subject since the last visit.
- The transition medication and the proper daily dosing is explained to the subject including confirmation that the subject understands the proper daily dosing;
- Dispensation of the transition study medication.

6.9. End of Study Visit, Post-treatment Follow-up (Visit 9, Day 120)

All randomized subjects will have a post-treatment contact at 30-35 days after the EOT visit to collect data on concomitant medications, SAEs, and other safety events of interest.

The following activities and/or assessments are performed and the outcomes recorded in the eCRF:

- Obtain INR and VKA dose information (VKA subjects only);
- Vital signs (heart rate, sitting blood pressure, body weight);
- Concomitant medications (changes);
- (S)AEs and endpoint events experienced by the subject since the last visit.

6.10. Missed Visits

Every effort should be made to ensure subjects return for their on-site visits. If the subject is unable to return for an on-site visit, the Investigator, or designee, must document in the eCRF the reason the subject was unable to complete the visit. The Investigator should also make every effort to contact the subject, within the visit window, to collect the subject's vital status as well as information related to potential AEs, safety data, and hospitalizations.

6.11. Modification of IC after Randomization

Subjects are scheduled to have regular study contacts every month until the End of Study Visit is completed (i.e., 30 days after the EOT Visit).

In accordance with the Declaration of Helsinki and other applicable regulations, a subject has the right to withdraw consent from study participation at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

This protocol makes a distinction between request to discontinue (1) any or all study medication, (2) on site visits, (3) telephone contacts, (4) collection of clinical follow-up data, (5) collection of vital status and (6) full withdrawal of IC.

During the treatment phase, all subjects are followed for 90 days irrespective of changes in the antithrombotic regimen. Henceforth, during interruption or following discontinuation of study medication, subjects continue to have regular study visits or telephone assessments until the 90-day EOT visit is completed.

If the subject cannot return for an in-person visit, a telephone visit is scheduled unless subject requests not to be contacted by telephone. Collection of available clinical data or vital status, either at the interventional center, at the referring hospital, with the general practitioner, or the municipal registries continues unless explicitly disallowed by subject.

Collected data up to the date of full withdrawal of IC are used in the final analysis.

Records in the eCRF document modifications to the IC as detailed above (including level and date of modification or withdrawal).

6.11.1. Subjects Lost to Follow-Up

All subjects should be encouraged to return for protocol-required on-site visits or telephone assessments for evaluation during the clinical follow-up. If a subject is unable to return for a clinic visit, subject should be contacted by telephone to obtain subject required information. All attempts should be documented in the source documents. If the subject does not respond to telephone calls, then the Investigator must send a certified letter to the subject. Only after failing to contact the subject at the final follow-up visit will the subject be considered lost to follow-up after last contact except for mortality if available via municipality registries. It must be a high priority to obtain at least survival data on all subjects lost to follow-up. When a subject is lost to follow-up an End-of-Study Form is completed.

6.12. End of Trial Definition

All randomized subjects will have a contact planned 30-35 days after the EOT visit, to collect data on targeted concomitant medications, SAEs, and other AESI. The final contact is the post-treatment follow-up visit scheduled at 30-35 days after the EOT visit. The study is deemed completed as soon as the final contact of the last subject is performed in all centers and in all participating countries.

7. OUTCOME ASSESSMENTS

7.1. Primary Efficacy Endpoint

Composite of all-cause death, stroke (ischemic, hemorrhagic, or undetermined), and Major Bleeding (ISTH definition), analyzed as time to first occurrence of any component.

7.2. Primary Safety Endpoint

Major Bleeding (ISTH definition), analyzed as time to first occurrence of Major Bleeding.

7.3. Secondary Endpoints

Efficacy:

- Composite of all-cause death, stroke (ischemic, hemorrhagic, or undetermined, according to alternative definition (1); see Section 7.4.2 for details) and Major Bleeding (ISTH definition)
- Composite of stroke (ischemic, hemorrhagic, or undetermined) SEE, and CV mortality
- Composite of stroke (ischemic, hemorrhagic, or undetermined) SEE, and all-cause mortality
- Composite of stroke (ischemic, hemorrhagic, or undetermined) and TIA
- Stroke (ischemic, hemorrhagic, or undetermined)
- Stroke (ischemic)
- Stroke (hemorrhagic)
- Stroke (undetermined)
- SEE
- TIA
- Fatal stroke (ischemic, hemorrhagic, or undetermined)
- Non-fatal stroke (ischemic, hemorrhagic, or undetermined)
- Disabling stroke (ischemic, hemorrhagic, or undetermined)
- Non-disabling stroke (ischemic, hemorrhagic, or undetermined)

Safety:

- Major Bleeding (defined by TIMI, BARC (2 or higher))
- Major and Clinically Relevant Non-Major (CRNM) Bleeding (ISTH definition)
- CRNM Bleeding (ISTH definition)
- Minor Bleeding (ISTH definition)
- Any Bleeding
- ICH

- Life-threatening bleeding
- Fatal Major Bleeding (ISTH definition)
- Non-fatal Major Bleeding (ISTH definition)
- Fatal Major Bleeding (defined by TIMI, BARC [2 or higher])
- Non-fatal Major Bleeding (defined by TIMI, BARC [2 or higher])
- Safety parameters such as AEs, SAEs, laboratory parameters, ECG and vital signs.

All adjudicated endpoints are analyzed as time to first occurrence of any of its components.

For all endpoints blindly adjudicated by the CEC, the CEC's interpretation prevails and is used in the statistical analyses.

7.3.1. Other Endpoints

- Relevant HEOR parameters:
 - Number of subjects with cancellation of ablation procedure due to inadequate anticoagulation
 - Number of hospital admissions due to CV causes (beyond ablation procedure), including but not limited to overall, for bleeding, SEE, venous thrombosis, etc. Remark: Hospital admissions due to CV causes include, but are not limited to ED, ICU, CV ward.
 - Mean length of stay associated with the different type of hospital admissions, such as ED, ICU and CV wards
 - Additional outpatient physician or nurse visits that are CV event related outside scheduled visits as defined by study protocol
- Silent cerebral lesions as defined by DW-MRI post ablation procedure (at preselected centers)
- Cardiac markers

7.4. Endpoint Definitions

All suspected clinical endpoints are adjudicated by an independent CEC (see Section 16.1.2) without knowledge of the actual assigned treatment. Main adjudication criteria are mentioned below. Further details on these definitions and how they will be assessed are provided in the CEC Charter.

The requirements for collecting and submitting the source documents for appropriate adjudication of the reported primary and secondary endpoint events will be provided to the sites/Investigators separately in the Study Operations Manual.

For all endpoints blindly adjudicated by the CEC, the CEC's interpretation prevails and is used in the statistical analyses.

7.4.1. Bleeding

Bleeding will be classified according to the ISTH definitions (16, 17). Bleeding events will also be classified according to BARC (18) and TIMI (22, 23) classifications for descriptive purposes only (see Section 16.3 for further details)

7.4.2. Efficacy Endpoint Definitions

The following efficacy endpoint definitions will be applied:

- A **stroke** is defined by an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. The event classifies as a stroke rather than a TIA based on any of the following:
 - Duration of neurological dysfunction >24 hours.
 - Duration of neurological dysfunction <24 hours in case of imaging-documented new hemorrhage or infarction.
 - A neurological dysfunction resulting in death (24).Stroke will be sub-divided into ischemic, hemorrhagic or undetermined. Stroke is categorized as disabling and non-disabling stroke using the modified Rankin Scale (mRS) score.
- **TIA** is defined by any neurological dysfunction not satisfying the above criteria for stroke, specifically if lasting <24 hours without imaging-documented acute brain infarction.

These definitions of TIA and stroke widely correspond with the “Updated standardized endpoint definitions for transcatheter aortic valve implantation” published by the VARC-2 group and with those “Definitions for Cardiovascular Endpoint Events in Clinical Trials” published by an ACC/AHA task force (25, 26).
- An **alternative definition of stroke** will be applied defining stroke as an abrupt onset, over minutes to hours, of a focal neurological deficit in the distribution of a single brain artery that is not due to an identifiable nonvascular cause (i.e., brain tumor or trauma), and that either lasts at least 24 hours or results in death within 24 hours of onset (1).

Corresponding to this **alternative definition**, **TIA** is defined as an abrupt onset, over minutes to hours, of a focal neurological deficit in the distribution of a single brain artery, that lasts less than 24 hours and is not due to an identifiable non-vascular cause (i.e., brain tumor or trauma) and does not satisfy the stroke definition above (1).
- An **SEE** is defined as an arterial embolism resulting in clinical ischemia, excluding the central nervous system (CNS), coronary and pulmonary arterial circulation (1).
- **CV mortality**, defined as cardiac or vascular death according to Academic Research Consortium (ARC) (27).

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS.

8.1. Pharmacokinetic Variable(s)

Not applicable.

8.2. Cardiac Markers

Evidence suggests that the cardiac biomarkers N-terminal fragment B-type natriuretic peptide (NT-proBNP) and cardiac troponin high sensitivity (cTn-hs) are independently associated with risk of stroke in AF (28). Non-genetic cardiac biomarkers such as NT-proBNP and cTn-hs will be analyzed in all patients at screening/randomization.

The results will be reviewed and compared to the central laboratory's normal ranges.

9. SAFETY ASSESSMENTS

Safety assessments that are components of the study endpoint assessments (e.g. bleeding endpoints) are detailed in Section 7.4 and must be collected in the AE/Outcome eCRF page(s).

9.1. Adverse Event Collection and Reporting

All clinical AEs (see Section 9.2 for definitions) occurring after the subject signs the ICF and up to 30 days after the last dose of study medication (ie, the follow-up period), whether observed by the Investigator or reported by the subject, will be recorded on the AE eCRF page. Medical conditions (including laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to IC will be recorded as part of medical history.

All AEs, SAEs, AESIs are to be reported according to the procedures in Section 9.5.

All laboratory results, vital signs, and ECG results or findings should be appraised by the Investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or ECG findings (i.e., not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, dose reduction, require corrective treatment, or constitute an AE in the Investigator's clinical judgment.

At each visit, the Investigator will determine whether any AEs have occurred by evaluating the subject. AEs may be directly observed, reported spontaneously by the subject or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Sections 9.2 and 9.3. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the ICF) procedures or treatments requiring hospitalization for pre-existing conditions that do not worsen in severity should not be reported as SAEs (see Section 9.2 for Definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any serious, untoward event that may occur subsequent to the reporting period that the Investigator assesses as related to study drug should also be reported and managed as an SAE.

9.2. Definitions

9.2.1. Adverse Event

Any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

9.2.2. Unexpected Adverse Event

An unexpected AE is an AE, the nature or severity of which is not consistent with the reference safety information of any of the study medication. The designation of expected or unexpected must be decided from the perspective of previously described AEs, not on the basis of what might be anticipated from pharmacological properties of a medicinal product. The investigator can provide his judgement on the expectedness/unexpectedness of a reported AE to the sponsor and this will be taken into account for the sponsor's judgement of expectedness. However, the final determination of expectedness is the responsibility of DSE and not the Investigator.

9.2.3. Expected Adverse Event

An expected AE is an event which is described in the reference safety information of the study drugs in nature, severity or incidence.

9.2.4. Serious Adverse Event

An SAE or reaction is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

OR

- is any other medically important condition (see below).

Note: Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples include allergic bronchospasm, convulsions, and blood dyscrasias or development of drug dependency or drug abuse.

Note:

- A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE.
- Treatment requiring hospitalizations for pre-existing conditions which do not worsen in severity are not SAEs.

9.2.5. Adverse Events of Special Interest

9.2.5.1. Combined Elevations of Aminotransferases and Bilirubin

There was no clinically concerning signal of drug-induced liver injury associated with edoxaban based on the extensive global Phase 3 experience involving over 34,100 edoxaban subject-years exposure (with median drug exposure of ~2.5 years among ~14,000 edoxaban subjects). However, there will be ongoing monitoring of hepatic events, including combined elevations of aminotransferases and bilirubin (ALT or AST >3x ULN with simultaneous TBL >2x ULN), particularly those without evidence of cholestasis (ALP \geq 2x ULN is considered evidence of possible cholestasis) and without alternative etiology for hepatocellular damage.

Combined elevations of aminotransferases and bilirubin, either serious or non-serious and whether or not causally related, should always be reported to the Sponsor as soon as possible following the procedures outlined in Section 9.5 for SAE reporting.

In cases of liver laboratory abnormalities, or evidence of liver dysfunction, it is important to ensure that the etiology of liver injury is identified and study subjects are monitored until the liver laboratory assessments return to normal.

9.3. Classification for AE assessment

9.3.1. Severity Assessment

The severity of an AE is graded as follows:

- Mild: Discomfort noted, but no disruption of normal daily activity.
- Moderate: Discomfort sufficient to reduce or affect normal daily activity.
- Severe: Inability to work or perform normal daily activity.

9.3.2. Causality Assessment

The Investigator should assess causal relationship between an AE and the assigned anticoagulant-based regimen (i.e., edoxaban-based or VKA-based) on the basis of his/her clinical judgment and the following definitions. The causality assessment should be made based on the available information and can be updated as new information becomes available.

- 1 = Related:
The AE follows a reasonable temporal sequence from the assigned anticoagulant-based regimen administration, and cannot be reasonably explained by the subject's

clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

The AE follows a reasonable temporal sequence from the assigned anticoagulant-based regimen administration, and is a known reaction to any of the study medications (i.e. the components of each study regimen) under study or its chemical group, or is predicted by known pharmacology.

- 2 = Not Related:

The AE does not follow a reasonable sequence from the assigned anticoagulant-based regimen administration, or can be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

9.3.3. Action Taken Regarding the Assigned Antithrombotic Regimen

For each study treatment, the action taken after an AE must be recorded in the eCRF as delineated below:

1 = Dose Not Changed: No change in dosage was made.

2 = Drug Withdrawn: Permanently stopped.

3 = Dose Reduced: The dosage was reduced.

4 = Drug Interrupted: Temporarily stopped.

5 = Dose Increased: The dosage was increased.

9.3.4. Other Action Taken for Event

1 = None: No treatment was required.

2 = Concomitant medication required: Prescription and/or over-the-counter medication were required to treat the AE.

3 = Concomitant medication permanently discontinued: Prescription and/or over-the-counter medication other than the assigned anticoagulant-based regimen was permanently discontinued due to the AE.

4 = Concomitant medication temporarily interrupted: Prescription and/or over-the-counter medication other than the assigned anticoagulant-based regimen was temporarily interrupted due to the AE.

5 = Other.

9.3.5. Adverse Event Outcome

1 = Recovered/Resolved: The subject fully recovered from the AE with no residual effect observed.

2 = Recovered/Resolved with Sequelae: The residual effects of the AE are still present and observable. Include sequelae/residual effects.

3 = Not Recovered/Not Resolved: The AE itself is still present and observable.

4 = Fatal

5 = Unknown

The Investigator should follow subjects with AEs until the event has resolved or the condition has stabilized. In case of unresolved AEs including significant abnormal laboratory values at the end of study assessment, these events will be followed up until resolution or until they become clinically not relevant.

9.4. Timing of Adverse Event Reporting

All AEs must be recorded and reported from the stated starting point of the clinical trial (immediately after signing IC) including AEs taking place during the administration of other drugs. Even if the subject has not yet received the investigational treatment, untoward medical occurrences have to be treated as AEs.

The period of AE reporting is defined as follows:

AEs that occur within 30 days after the last dose of the assigned study treatment, which are reported to the Investigator (regardless of the date of a follow-up visit) must be recorded in the eCRF.

9.5. Reporting SAEs/AEs

9.5.1. Documentation

To effectively evaluate the safety profile of the study treatments, this study will report all (S)AEs occurring after the subject signs the IC and up to 30 days after the last dose of the assigned treatment, whether observed by the Investigator or reported by the subject. All AEs will be recorded on the AE/Outcome eCRF page(s) and include:

- Any components of the study endpoint assessments (see Section 7);
- AE that meet seriousness criteria (see Section 9.2.4);
- AE that result in interruption or discontinuation of the assigned study treatment;
- AE that meet the criteria for AESI (see Section 9.2.5);
- Any other AE.

All laboratory results and vital signs should be evaluated by the Investigator regarding clinical significance. Isolated abnormal laboratory results or vital sign findings that are not part of a diagnosis should be reported as AEs or SAEs. Medical conditions (including laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to IC will be recorded as part of medical history.

All SAEs are to be reported according to the procedures in Section 9.5.2. Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the

diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE. For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization).

AEs may be directly observed, reported spontaneously by the subject or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Sections 9.2 and 9.3. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature.

In case of an occurrence of an (S)AE, the Investigator applies the following rules:

- Ensure appropriate medical treatment and decide whether to discontinue or interrupt any of the study medications.
- Complete the initial AE/Outcome eCRF page upon event awareness.
- Record the event, its management, and outcome in the eCRF page.
- For SAEs, report in the eCRF **within 24 hours** of receiving knowledge of the occurrence. In the event that all the required information is not available, the information which is available is to be sent without delay (within 24 hours), and the outstanding data relayed as soon as available thereafter. Answer any queries related to the reported SAE as soon as possible.
- For AESIs, report **within 24 hours** of receiving knowledge of the occurrence as defined for SAEs above.
- For AEs, obtain all data required incl. any information which, is only available after considerable delay (i.e. hospital reports, outcomes, resolution end dates), **as soon as available**
- Components of the study endpoint assessments which result in death must be reported as SAEs **within 24 hours** of the Investigator's awareness.

9.5.2. Notifying Regulatory Authorities, Investigators and Institutional Review Board/Independent Ethics Committee

Detailed SAE processing, distribution and reporting will be laid out in sponsor's SAE Flow Plan.

Sponsor and/or Contract Research Organization (CRO) will inform Investigators, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and regulatory authorities of any Suspected Unexpected Serious Adverse Event Reactions (SUSARs) occurring in the study or other sponsor studies of the investigational product, as appropriate per local reporting requirements.

In the EU countries, it is the Sponsor's responsibility to report SUSARs to regulatory authorities and IECs.

Study endpoints are clinically anticipated events in AF subjects receiving antithrombotic therapy and will be periodically reviewed by the DSMB in a blinded manner to ensure prompt identification of any clinically concerning safety issues.

9.6. Reporting of Pregnancy/ Exposure in Utero

The sponsor or designee must be notified of any subject that becomes pregnant while participating in a clinical study. All pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the Investigator, or designee, to report any pregnancy in a subject, which occurs during the study.

If any study subject becomes, or is found to be, pregnant while receiving, or within 30 days of discontinuing the investigational product, the Investigator should contact the Medical Monitor to discuss subject management and receive further information. Notification of the pregnancy should be submitted in the eCRF (AESIs) within 24 hours and reported using Exposure in Utero Reporting form (paper form).

If it is the partner, rather than the subject, who is found to be pregnant, the Exposure in Utero Reporting Form should be completed with the subjects' ID number, and year of birth. Details regarding the partner should be entered in the narrative Section of the Exposure in Utero Reporting form if a consent of the trial subject's partner has been obtained by the Investigator.

If the pregnancy is to be terminated, the anticipated date of termination should be provided. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify the Sponsor. If the outcome of the pregnancy meets the **criteria for immediate classification as a SAE (i.e. post-partum complications, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus)**, the Investigator should follow the procedures for reporting an SAE. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy in a follow-up Exposure in Utero Reporting Form.

9.7. Clinical Laboratory Evaluations

Refer to the Laboratory Manual for detailed instructions of sample collection, storage, and shipment. The results will be reviewed and compared to the central laboratory's normal ranges. The visits at which these samples will be collected are shown in the schedule of assessments (Section 16.9).

The following safety laboratory evaluations are performed in individual blood samples.

- Liver Function Panel
 - TBL (conjugated/unconjugated performed when total serum bilirubin ≥ 2 mg/dL)
 - ALT
 - AST
 - ALP

- Serum Chemistry Panel
 - Creatinine
- Hematology Panel including
 - WBC count with differential if elevated
 - Red Blood Cell counts and status (e.g., hemoglobin, hematocrit)
 - Platelet count
- INR (only in subjects randomized to VKA)

In women of childbearing potential, a urine test for pregnancy will be performed at screening, at baseline, and at Day 30. Furthermore, pregnancy tests are carried out whenever there are clinical indications for the existence of a pregnancy.

All other assessments are collected from local laboratory results for tests done as part of routine care. Local laboratory assessments are used to verify eligibility and for parameters that require monitoring according to local routine.

9.8. Vital Signs

The following parameters are recorded for vital signs:

- Heart Rate (at all visits post screening)
- BP, sitting diastolic and systolic BP (at all visits)
- Weight (at all visits)
- Height (only at randomization)

9.9. Electrocardiograms

Twelve-lead ECGs are collected according to the schedule of assessments (Section 16.9). Investigational sites will utilize local ECG equipment and record pertinent information in the eCRF while preserving all recorded ECG tracings as subject source documentation.

9.10. Physical Examination Findings

The Investigator or a licensed team member performs targeted physical examination at Screening. This physical examination consists of assessment of each of the relevant (including but not limited to cardiac, neurologic, pulmonary, GI) major body systems. Any clinically significant findings must be recorded in the eCRF under medical history.

9.11. Magnetic Resonance Imaging: Diffusion-Weighted Imaging

Procedure-associated stroke, as the most severe disabling complication, is rare and occurs in less than 1% of subjects undergoing ablation. Magnetic resonance imaging (MRI) identified new embolic lesions in 40-50% of cases. Positive MRI findings may occur in patients without apparent neurological deficit and are therefore classified as “asymptomatic” or “silent”. Silent cerebral events (SCE) are not unique to AF ablation but have been identified after nearly any CV interventions, including coronary angiography in 15%, valve surgery in 42%, and both on-and off-pump CABG in 22%. As a consequence, SCE or silent cerebral lesions (SCL) have been termed the “embolic fingerprint” of a specific CV intervention (29).

In comparative studies, SCE (DWI-MRI positive only) appear to be approximately 3 times more common compared to using a definition of silent cerebral lesions (SCL; without fluid attenuated inverse recovery sequence [FLAIR] positivity). Whereas the FLAIR sequence may turn positive within days after the ischemic event, SCE definition is highly sensitive for early phases of ischemic brain damage.

DW-MRI will be performed in a subset of study sites in order to assess the incidence of SCE/SCL under the NOAC edoxaban as compared to current standard of care management of uninterrupted VKA in patients undergoing an ablation procedure.

The MRI outcomes of interest include but are not limited to: acute DWI infarct present or not, number of acute DWI infarcts present, volume of each acute DWI infarct, total acute DWI infarct volume, white matter lesion volume on T2/FLAIR, grey matter (GM) lesion volume (acute and chronic infarcts) on T2/FLAIR.

The MRI protocol will be provided in its entirety in the Trial Site Imaging Manual and will be adapted according to the MRI vendor and specifications.

10. STATISTICAL METHODS

A general description of the statistical methods used is outlined below. A more detailed statistical analysis plan (SAP) will be provided in a separate document. The SAP will also accommodate protocol amendments or unexpected issues in study execution or data that affect planned analyses, and will provide more details on the analytic approaches, coding guidelines, censoring of time-to-event variables, and output tables and figures. To preserve the integrity of the statistical analysis and clinical study conclusions, the SAP will be finalized prior to database lock.

10.1. Analysis Sets

10.1.1. Intent-to-Treat Analysis Set

The Intent-to-treat (ITT) analysis set consists of all randomized subjects irrespective whether they received a single dose of the randomized study regimen or not.

Analyses will be based on the randomized treatment regimen even if a subject inadvertently receives the incorrect drug(s) or dosage or has his/her edoxaban dose adjusted (decreased/increased) one or more times during the study. The reference date for consideration of endpoints is the date and time of randomization.

10.1.2. Modified Intent-to-Treat Analysis Set

The modified Intent-to-Treat (mITT) analysis set consists of all randomized subjects who received at least one dose of study edoxaban or study VKA according to IXRS assignment.

Analyses will be based on the randomized treatment regimen even if a subject inadvertently receives the incorrect drug(s) or dosage or has his/her edoxaban dose adjusted (decreased/increased) one or more times during the study. The reference date for consideration of endpoints is the date and time of first intake of study edoxaban or study VKA.

10.1.3. Per Protocol Analysis Set

The Per Protocol (PP) analysis set consists of all randomized subjects who received at least one dose of the study regimen and do not have any of the following major protocol violations:

- Not undergoing a catheter ablation
- No AF
- Known contraindication for OAC
- A major violation of the inclusion criteria
- A major violation of the exclusion criteria

The full list of major violations will be described in the SAP and finalized before data base lock.

The list and the exclusions will be confirmed in a blinded way, i.e. without knowledge of the randomized study regimen and of the clinical outcomes.

Analyses will be based on the randomized treatment regimen, even if a subject inadvertently receives the incorrect drug(s) or dosage or has his/her edoxaban dosage adjusted (decreased/increased) one or more times during the study. The reference date for consideration of endpoints is the date and time of first intake of study edoxaban or study VKA.

10.1.4. Safety Analysis Set

The Safety (SAF) analysis set consists of all randomized subjects who received at least one dose of the study edoxaban or study VKA according to IXRS assignment.

Analyses will be based on the randomized treatment regimen, even if the subject's edoxaban dosage is adjusted after randomization, unless a subject inadvertently receives the incorrect drug(s) or dosage during the entire study, in which case the subject will be grouped according to the treatment actually received. The reference date for consideration of endpoints is the date of first study medication intake.

Note: This SAF analysis set will be used for the safety parameters (e.g. AEs, vital signs, laboratory parameters, etc.) as described under Section 9.

10.2. General Statistical Considerations

According to the objectives of this study, the statistical analysis should be interpreted in a purely exploratory-descriptive way. No formal confirmatory statistical testing is planned.

All analyses will be performed on observed data only. No missing data will be imputed. Data on subjects who do not reach a specific endpoint will be censored in the corresponding statistical analyses.

Raw data will be presented with the exact precision (decimal points) with which it was collected.

The p-values will be presented in the end-of-text tables exactly as they are in supporting statistical documents (4 decimal points). The text and in-text tables will display p-values with three decimal places, as long as, the decision for statistical significance will not be changed by rounding.

The number of decimal places to display for calculated data will be determined by the scale of measurement. No decimal places will be displayed if the smallest calculated value is ≥ 100 ; One (1) decimal place will be displayed when all calculated values are within the interval (10, 100), with 10 being inclusive; Two (2) decimal places will be displayed when all calculated values are within (1, 10), with 1 being inclusive; and so on for even smaller scales of measurement. Percentages will be reported with exactly one decimal place.

For continuous variables, statistical summaries will include n (number of subjects with non-missing data), mean, median, standard deviation, minimum and maximum. Means and medians will be displayed to one more decimal places than the raw or calculated data; standard deviation and other dispersion statistics will have two more decimal places; and minimum and maximum values will be displayed to the same number of decimal places as the raw or calculated data.

For categorical variables, statistical summaries will include counts and percentages. Percentages will be reported with exactly one decimal place. In general, percentages are based on the total number of subjects with information available (ie non-missing data). For AE and incidence based

analyses, percentages will be based on the total number of subjects in the analysis set of interest and in that treatment regimen.

The statistical data analysis will be performed by a CRO under the guidance of the study biostatistician using SAS Version 9.3 or higher.

Definition of terms:

‘Overall Study Period’: This period is defined as the time from the reference date (date and time of randomization or date and time of first dose of study medication) to Day 90/EOT.

‘Overall Study Period + 30 days’: This period is defined as the time from the reference date (date and time of randomization or date and time of first dose of study medication) to Day 90/EOT + 30 days.

‘Post-ablation Study Period’: This period is defined as the time from the end of the catheter ablation procedure to Day 90/EOT.

‘Post-ablation Study Period + 30 days’: This period is defined as the time from the end of the catheter ablation procedure to Day 90/EOT + 30 days.

Follow-up is censored at the last date of known follow-up status in subjects with incomplete follow-up. Investigators are instructed to complete follow-up as much as possible irrespective of changes or discontinuation of study medication.

All adjudicated endpoints are analyzed as time to first occurrence of any of its components.

For all specific endpoints blindly adjudicated by the CEC, the CEC’s interpretation prevails and is used in the statistical analyses.

The analysis set and analysis period to be used for the main analysis of the various adjudicated endpoints is presented below:

Endpoint(s)	Primary analysis set	Primary analysis period
Primary	PP	post-ablation period
Primary safety	mITT	overall study period
Secondary efficacy	PP	post-ablation period
Secondary safety	mITT	overall study period

However, in supplemental analyses, other combinations of analysis sets and analysis periods may be considered to evaluate the robustness of the main analyses on adjudicated efficacy and/or safety endpoints. Details on these analyses will be described in the SAP.

10.3. Study Population Data

Subject disposition will be summarized for each randomized treatment and in total for the ITT analysis set. The number of subjects for each defined analysis set by treatment group will also be tabulated.

The demographic and baseline characteristics including baseline disease status will be summarized descriptively by treatment group for the ITT, mITT, PP and SAF analysis sets.

Exposure to study medication (edoxaban and VKA) will be summarized using descriptive statistics by treatment group for the mITT, PP and SAF analysis sets. Interruptions and permanent discontinuations (see Section 5.2.3) will be summarized by treatment group for the same analysis sets.

The time in therapeutic range (TTR) (INR: 2.0-3.0, inclusive) will be estimated for each subject randomized to the VKA arm using the interpolation method of Rosendaal (30).

10.4. Statistical Analysis

10.4.1. Analysis of Adjudicated Efficacy Endpoints

The following endpoints are considered as efficacy endpoints:

- Composite of all-cause death, stroke (ischemic, hemorrhagic, or undetermined) and Major Bleeding [ISTH definition] (*primary efficacy endpoint*)
- Composite of all-cause death, stroke (ischemic, hemorrhagic, or undetermined, according to alternative definition (1); see Section 7.4.2. for details) and Major Bleeding (ISTH definition)
- Composite of stroke (ischemic, hemorrhagic, or undetermined) SEE, and CV mortality
- Composite of stroke (ischemic, hemorrhagic, or undetermined) SEE, and all-cause mortality
- Composite of stroke (ischemic, hemorrhagic, or undetermined) and TIA
- Stroke (ischemic, hemorrhagic, or undetermined)
- Stroke (ischemic)
- Stroke (hemorrhagic)
- Stroke (undetermined)
- SEE
- TIA
- Fatal stroke (ischemic, hemorrhagic, or undetermined)
- Non-fatal stroke (ischemic, hemorrhagic, or undetermined)
- Disabling stroke (ischemic, hemorrhagic, or undetermined)
- Non-disabling stroke (ischemic, hemorrhagic, or undetermined)

For all endpoints blindly adjudicated by the CEC, the CEC's interpretation prevails and is used in the statistical analysis.

For each of the primary and secondary efficacy endpoints, appropriate summary statistics (e.g. event rate) including 95% confidence interval (CI) will be provided.

For each of the endpoints, the time from reference date to the first occurrence of an event (based on CEC adjudication) is analyzed using a Cox proportional hazard model with treatment regimen as a factor, to provide point estimates and 95% CI for the hazard ratio (HR). Depending on the analysis period used in the statistical analysis, subjects without an occurrence of an event will be censored at the last date of the analysis period or at the last date of known outcomes status. The latter is determined on an individual basis for subjects with incomplete follow-up.

The parameter estimate β ($= \ln(\text{HR})$), its standard error, p-value, and 95% confidence limits are calculated according to the maximum partial likelihood method (ML), with Breslow's approximation for ties (SAS PHREG procedure).

For time to first event analyses based on the 'overall study period', 'overall study period + 30 days', 'post-ablation study period' and 'post-ablation study period + 30 days', cumulative event rates over time are summarized using the Kaplan-Meier method.

10.4.2. Analysis of Adjudicated Safety Endpoints

The following endpoints are considered as safety endpoints:

- Major Bleeding [ISTH definition] (*primary safety endpoint*)
- Major Bleeding [defined by TIMI, BARC (2 or higher)]
- Major or CRNM bleeding [ISTH definition]
- CRNM bleeding [ISTH definition]
- Minor bleeding [ISTH definition]
- Any bleeding
- ICH
- Life-threatening bleeding
- Fatal Major Bleeding [ISTH definition]
- Non-fatal Major Bleeding [ISTH definition]
- Fatal Major Bleeding [defined by TIMI, BARC (2 or higher)]
- Non-fatal Major Bleeding [defined by TIMI, BARC (2 or higher)]

All these endpoints will be analyzed using the same methodology as described in Section 10.4.1.

10.4.3. Analysis of Other Parameters

All parameters mentioned in Section 7.3.1 will be summarized descriptively by treatment regimen for the ITT, mITT, and PP analysis sets.

10.4.4. Safety Analyses

10.4.4.1. Adverse Event Analyses

Adverse events meeting the criteria defined in Section 9.1 will be recorded in the eCRF and coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.1 or newer.

Treatment-emergent adverse events (TEAEs) are defined as events which start on or after any first dose of the assigned study medication regimen or started prior to but then worsened after any first dose of the assigned study medication regimen. An AE that occurs more than 30 days after the date of the last dose of the assigned study medication regimen will not be counted as a TEAE.

The AE analysis will be based on the SAF analysis set. TEAEs will be summarized by treatment group. The incidence of TEAEs will be presented by treatment group, by relationship to the assigned study regimen, and by severity. If more than one AE is coded to the same preferred term for the same subject, the subject will be counted only once for that preferred term using the greatest severity and strictest causality for the summarization by severity and causal relationship. Frequent TEAEs (reported by at least 5% resp. 1% of subjects in any treatment group) will be summarized by regimen group.

The incidence of death, SAEs, drug-related SAEs, and AEs leading to permanent discontinuation of the assigned study regimen will be summarized. All AEs recorded will be included in a data listing and a listing to display the coding of AEs will be prepared as well.

10.4.4.2. Clinical Laboratory Evaluation Analyses

The clinical laboratory evaluations for each scheduled test and the change from baseline will be summarized for the SAF analysis set by treatment group. Shift tables (in categories of low, normal, and high) will be provided for each treatment regimen for selected laboratory parameters. Also, the number and percentage of subjects with clinically relevant abnormal laboratory values while on study drug will be calculated for each treatment regimen for selected laboratory parameters. All abnormal laboratory values will be presented in a listing. More details will be provided in the SAP.

10.4.4.3. Vital Signs Analyses

Vital signs at each evaluation point and the change from baseline will be summarized for the SAF analysis set by treatment group. More details will be provided in the SAP.

10.4.4.4. Electrocardiogram Analyses

The ECG evaluations at randomization, cardiac ablation visit, hospital discharge, Day 30 and Day 90 will be summarized by treatment group based on SAF analysis set. More details on the ECG analysis will be provided in the SAP.

10.4.4.5. Physical Examination Analyses

A physical examination will only be performed at the Screening visit.

Counts and percentages of physical examination findings will be summarized by treatment regimen based on SAF analysis set.

10.4.5. Other Analyses

Details on any other analyses, if applicable, will be given in the SAP.

10.5. Interim Analyses

Not applicable.

10.6. Data and Safety Monitoring Board

There will be an independent DSMB to protect the rights, safety and well-being of subjects participating in this study. The DSMB will be involved in the management of this clinical study serving as the safety monitoring advisory group for the study. The primary role of the DSMB will be to examine the safety data (incidence of Major Bleedings, CRNM bleeding, or other safety endpoints, or suspected related (S)AEs) on an ongoing manner and to alert the Executive Committee in case of any clinically concerning safety issues.

The frequency and extent of the data reviews by the DSMB, details about the reviews and stopping rules or criteria for evaluating need for study protocol modifications will be described and specified in the DSMB charter.

10.7. Sample Size Determination

The primary efficacy endpoint is the incidence of a composite of all-cause death, stroke (ischemic, hemorrhagic or undetermined), and Major Bleeding events (ISTH definition) during the period from the end of the catheter ablation procedure to Day 90/EOT.

A rate of up to 3% of the combined primary endpoint can be expected in the VKA arm as observed from published studies and retrospective analyses. Based on a very recent study involving uninterrupted anticoagulation with VKA, a slightly lower rate of the combined endpoint of about 2% can be anticipated (VENTURE AF [5]).

In a large retrospective case series, fatal outcome in catheter ablation of AF has been found to occur in 0.1% (31). Neurological complications (postoperative stroke/TIA) were reported in 1.0% of patients undergoing ablation in one large survey (32). In another survey, stroke (0.23%) and

TIA (0.71%) have been reported separately (9). In the COMPARE study, patients under continued anticoagulation with warfarin experienced 0.25% strokes (14). In a more recent study involving NOACs, a rate 2.1% of strokes has been found under VKA (10). Major Bleeding complications have occurred with incidences of 3.38% (postop hemorrhage) and 0.58% (postop hemorrhage requiring transfusion) in a large survey (32). An incidence of 0.38% of Major Bleeding events has been reported in the COMPARE study under continued administration of warfarin (14). Under interrupted VKA, the incidence of Major Bleeding was 4.2% in another recent study (10). In a further recent study investigating two regimens of uninterrupted anticoagulation, 2.2% of Major Bleeding events occurred in the warfarin group (11). In a meta-analysis covering a broader range of patients undergoing device implantation, 2.8% of patients were suffering from Major Bleeding events under continued oral anticoagulation (33).

Based upon this predicted rate, a formal sample size determination based on non-inferiority or superiority of edoxaban versus VKA is not feasible. The study size is planned based upon the primary composite endpoint to include an adequate number of subjects that will provide the expected incidence rates on the primary endpoint. Therefore, the plan is to include 450 subjects in the PP study population (subjects who have undergone the ablation procedure and completing the study). In order to achieve this, approximately 560 subjects will need to be enrolled in the study. The study will be stopped once the number of 450 subjects belonging to the PP analysis set is reached.

11. DATA INTEGRITY AND QUALITY ASSURANCE

The Investigator/investigational site will permit study-related monitoring, audits, IEC review and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify and reproduce any records and reports that are important to the evaluation of a clinical study.

11.1. Monitoring and Inspections

The Sponsor, site monitors, and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (e.g., eCRFs, source data, and other pertinent documents).

The monitor is responsible for visiting site(s) at regular intervals (as detailed in the Monitoring Plan) throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to International Conference on Harmonization Good Clinical Practice (GCP) and local regulations on the conduct of clinical research. The monitor is responsible for inspecting the eCRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs.

The monitor will communicate deviations from the protocol, SOPs, GCP and applicable regulations to the Investigator and will ensure that appropriate action designed to prevent recurrence of the detected deviations is taken and documented.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed and documented.

In accordance with GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from sponsor. Inspection of site facilities (e.g., pharmacy, drug storage areas, laboratories, etc.) and review of study related records will occur in order to evaluate the study conduct and compliance with the protocol, GCP, and applicable regulatory requirements.

In the event that a regulatory authority informs the Investigator that it intends to conduct an inspection, sponsor shall be notified immediately.

11.2. Data Collection

The eCRF completion should be kept current to enable the monitor to review the subject's status throughout the course of the study. The eCRF is completed by the Investigator or qualified designee. Completed eCRFs are reviewed and e-signed by the Investigator (or by a sub-Investigator, with permission of the Sponsor).

11.3. Data Management

Each subject will be identified in the database by a unique subject ID number as defined by the sponsor.

To ensure the quality of clinical data across all subjects and sites, a Clinical Data Management review will be performed on subject data according to specifications given to the CRO. Data in the eCRF is vetted electronically by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated within the electronic data capture (EDC) application. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies.

Data received from external sources such as central labs will be reconciled to the clinical database. SAEs in the clinical database will be reconciled with the safety database.

11.4. Study Documentation and Storage

The Investigator will maintain a Signature List of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on eCRFs will be included on the Signature List.

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, X-rays, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (Trial Master File) of all study-related (essential) documentation, suitable for inspection at any time by representatives from sponsor and/or applicable regulatory authorities. Essential documents include:

- Subject files containing ICs, and supporting copies of source documentation as used for eCRFs completion. In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.
- Study files containing the protocol with all amendments, IB, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the IEC/IRB and Sponsor.
- Records related to the study medications delivered including acknowledgment of receipt at site, accountability records and final reconciliation and applicable correspondence.

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

Essential clinical trial documents (including case report forms) other than subject's medical files must be kept for at least 15 years after completion or discontinuation of the trial. Subject's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice. It is the responsibility of the sponsor to inform the Investigator/institution as to when the clinical trial documents no longer need to be retained.

No study document should be destroyed without prior written agreement between sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move

them to another location, he/she must notify DSE in writing of the new responsible person and/or the new location.

11.5. Record Keeping

Records of subjects, source documents, monitoring visit logs, data correction forms, eCRFs, inventory of study product, regulatory documents (e.g., protocol and amendments, IEC/IRB correspondence and approvals, approved and signed ICs, Investigator's Agreement, clinical supplies receipts, distribution and return records), and other sponsor correspondence pertaining to the study must be kept in appropriate study files at the site. Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by the institution or site policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

12. FINANCING AND INSURANCE

12.1. Finances

Prior to starting the study, the Principal Investigator and/or institution will sign a clinical study agreement with the sponsor or with an authorized representative of sponsor. This agreement will include the financial information agreed upon by the parties.

12.2. Reimbursement, Indemnity, and Insurance

Reimbursement, indemnity and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

The Sponsor provides insurance for study subjects to make available compensation in case of study-related injury.

13. PUBLICATION POLICY

A study site may not publish results of a study until after a coordinated multicenter publication has been submitted for publication or until one year after the study has ended, whichever occurs first. Therefore, the study site will have the opportunity to publish the results of the study, provided that sponsor and the executive committee has had the opportunity to review and comment on the study site's proposed publication prior to its being submitted for publication with the advice of company patent council and in accord with needs for subject protection.

14. ETHICS AND STUDY ADMINISTRATIVE INFORMATION

14.1. Compliance Statement, Ethics and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the ICH consolidated Guideline E6 for GCP (CPMP/ICH/135/95), and applicable regulatory requirement(s):

- European Commission Directive (2001/20/EC Apr 2001);
- European Commission Directive (2005/28/EC Apr 2005);
- European Data Protection Directive 95/46/EC;
- Other applicable local regulations.

14.2. Subject Confidentiality

The Investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP, the rules laid down for the protection of individuals with regard to the processing of personal data and the free movement of such data and other local regulations.

For EU study centers, the Sponsor will observe the rules laid down in the European Data Protection Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and the free movement of such data.

The Investigator must ensure that the subject's anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor, subjects should be identified by a unique subject ID number as designated by the sponsor. The Investigator must obliterate any private information contained on documents (e.g. name or address) prior to passing them on to the sponsor or CRO. Documents that are not for submission to either Sponsor or CRO (e.g., signed IC) should be kept in strict confidence by the Investigator.

In compliance with GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the subject's original medical records for verification of study-related procedures and data.

14.3. Informed Consent Procedure

Before a subject's participation in the study, it is the Investigator's responsibility to obtain freely given consent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any study drugs are administered. Subjects must have the opportunity to ask questions and receive satisfactory answers to their inquiries, and must have adequate time to decide whether or not to participate in the study. The written ICF is prepared in the local language(s) of the potential subject population.

14.4. Regulatory Compliance

The study protocol, subject information and consent form, the Investigator's Brochure, any subject diary card or written instructions to be given to the subject, available safety information, subject recruitment procedures, information about payments and compensation available to the subjects and documentation evidencing the Investigator's qualifications should be submitted to the IEC/IRB for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the SAP.

All subsequent substantial protocol amendments and changes to the ICF will be submitted to the IEC/IRB for approval. The Investigator should notify the IEC/IRB of deviations from the protocol or SAEs occurring at the site and other adverse event reports received from Sponsor/CRO, in accordance with local procedures.

As required by local regulations, the Sponsor's local Regulatory Affairs group or delegate will insure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to study initiation, and that implementation of changes to the initial protocol and other relevant study documents happen only after the appropriate notification of or approval by the relevant regulatory bodies.

14.5. Protocol Deviations

The Investigator conducts the study in compliance with the protocol agreed to by sponsor and, if required, by the regulatory authority(ies) and by the EC.

Actions taken to eliminate immediate subject hazard(s) that deviate from any protocol procedures are marked / flagged as a deviation. The sponsor and site monitor must be notified of all intended or unintended deviations to the protocol (e.g., inclusion/exclusion criteria, dosing) on an expedited basis. The Investigator, or person designated by the Investigator, should document and explain any deviation from the approved protocol and notify the EC of any protocol deviations in accordance with local procedures.

Even if a subject was ineligible or inadvertently received the incorrect drug or dosage, discontinued or interrupted the assigned treatment regimen, or refused to further undergo on-site visits, clinical follow-up data should still be collected up to Day 90 after catheter ablation (i.e., EOT).

14.6. Supply of New Information Affecting the Conduct of the Study

When new information becomes available that may adversely affect the safety of subjects or the conduct of the study, the Sponsor will inform all Investigators involved in the clinical study, ECs/IRBs, and regulatory authorities of such information, and when needed, will amend the protocol and/or subject information.

The Investigator should immediately inform the subject whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participation in the study. The communication should be documented on medical records, for example, and it should be confirmed whether the subject is willing to remain in the study.

If the subject information is revised, it must be re-approved by the IEC/IRB. The Investigator should obtain written informed consent to continue participation with the revised written information even if subjects were already informed of the relevant information. The Investigator or other responsible personnel who provided explanations and the subject should sign and date the revised ICF.

14.7. Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the Investigator by the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A substantial protocol amendment may be implemented after it has been approved by the IEC/IRB, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IEC/IRB within five working days. The sponsor will assure the timely submission of substantial amendments to regulatory authorities.

14.8. Address List

14.8.1. Sponsor

Daiichi Sankyo Europe GmbH
Zielstattstrasse 48
81379 Munich
Germany

14.8.1.1. DSE Project Leader

[REDACTED]


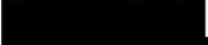
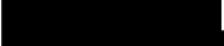

14.8.1.2. DSE Medical Expert

[REDACTED]

14.8.2. CRO

Chiltern International Sarl
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14.8.2.1. CRO Medical Monitor


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Canada Square Office House
Ganz u. 12-14, 4. emelet
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Phone: 
Mobile: 
Email: 

14.8.2.2. CRO Project Manager


Phone: 
Mobile: 
Fax: 
Email: 

14.8.3. Drug Safety

14.8.3.1. DSE




14.8.3.2. CRO


Phone: 
Fax: 
Email: 

14.8.4. Biostatistics & Data Management

14.8.4.1. DSE Data Management




14.8.4.2. DSE Biostatistician



14.8.5. Biological Specimens

<<Will be known only later>>

14.8.6. Interactive Web Voice Response System (IXRS)

Almac Clinical Services Limited
Seagoe Industrial Estate,
Craigavon, 9 Charlestown road BT63 5PW
Northern Ireland

14.8.7. Bioanalytical Laboratory

LabConnect LLC
605 First Avenue,
Suite 300, Seattle, WA 98104-2224
USA

14.8.8. eCRF Provider

Medidata Solutions
1301 Fannin Street
Suite 1295
Houston, Texas 77002
USA

14.8.9. Other

<< Will be known only later >>

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16. APPENDICES

16.1. Study Organization

16.1.1. Data and Safety Monitoring Board

There will be an independent DSMB to protect the rights, safety and well-being of subjects participating in the study. The DSMB consists of qualified scientists, who are not Investigators in the study and not otherwise directly associated with the sponsor, and has the primary role in examining the safety data and other pertinent data. The DSMB monitors study data in an un-blinded, ongoing manner and alerts the Executive Committee in case of any clinically concerning safety issues.

The frequency and extent of the data reviews by the DSMB, details about the reviews and stopping rules or criteria for evaluating need for study protocol modifications will be described and specified in the DSMB charter. The DSMB can recommend modification of the study protocol, or study, or treatment regimen to the Executive Committee based on pre-specified rules described in the DSMB charter.

All activities of the DSMB will be documented. This documentation will include data summaries and analyses (see Section 10.6) provided to the DSMB as well as minutes of the meetings. The documentation will remain confidential within the DSMB until the study is completed. An independent statistician who is not otherwise involved in the study will prepare the required data outputs and provide the outputs to the DSMB as per the DSMB charter.

16.1.2. Clinical Events Committee

An independent CEC reviews and adjudicates the following events in a blinded manner and without any knowledge of the subject's assigned treatment regimen:

- Major Bleeding;
- CRNM bleeding;
- Minor bleeding;
- Death from any cause;
- Suspected stroke;
- Suspected SEE;
- Suspected MI;
- Suspected TIA;

Details about the definitions of the endpoints (Section 7.4), endpoint sub-categories and other CEC processes are described in the CEC charter.

The single components of the composite primary (and secondary endpoints mentioned above are explored, as well as specific subcategories (e.g., ICH, ischemic stroke) and event classifications according to other definitions (e.g., BARC, TIMI).

16.1.3. Executive Committee

The Executive Committee will be responsible for the overall design, conduct, and supervision of the study, including the development of any protocol amendments. The Executive Committee will also review the progress of the study at regular intervals to ensure subject

safety and study integrity. The Executive Committee will be comprised of designated representatives from the study investigators, CRO, and Sponsor.

16.1.4. Operations Committee

The Operations Committee will be responsible for the ongoing monitoring of the study data and implementation of steps to improve the quality of the study conduct. The Operational Committee will be comprised of designated representatives of CROs and Sponsor and will report at regular intervals to the Executive Committee on the progress of the study.

16.2. Sub-study

Subjects in this study may participate in one sub-study. Dedicated sites are invited for participation according to sites capabilities to meet specific sub-study requirements and on the required number of observations. Currently, one sub-study is being considered involving DW-MRI.

16.3. Bleeding Criteria

Table 16.1: ISTH Bleeding Criteria

International Society on Thrombosis and Hemostasis (ISTH) Bleeding Criteria
Major Bleeding <ul style="list-style-type: none"> • Clinically overt bleeding that is associated with: <ul style="list-style-type: none"> ○ A fall in hemoglobin of 2 g/dL (1.24 mmol/L) or more, or ○ A transfusion of 2 or more units of whole blood or packed red blood cells, or ○ Symptomatic bleeding in a critical site or organ such as: intracranial, intraspinal, intraocular, retroperitoneal, pericardial, intra-articular, intramuscular with compartment syndrome, or ○ A fatal outcome
Clinically Relevant Non-Major (CRNM) Bleeding <ul style="list-style-type: none"> • Any sign or symptom of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of Major Bleeding but does meet at least one of the following criteria: <ul style="list-style-type: none"> ○ requiring medical intervention by a healthcare professional ○ leading to hospitalization or increased level of care ○ prompting a face to face (i.e., not just a telephone or electronic communication) evaluation.
Minor <ul style="list-style-type: none"> • Bleeding episodes not requiring any medical attention and therefore not meeting the criteria for major or clinically relevant non-Major Bleeding.
Refs 16, 17

Table 16.2: TIMI Bleeding Criteria

TIMI Non-Coronary Artery Bypass Graft (CABG) Related Bleeding:
1 Major <ul style="list-style-type: none"> • Any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo magnetic resonance imaging [MRI]) • Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥ 5 g/dL or a $\geq 15\%$ absolute decrease in hematocrit • Fatal bleeding (bleeding that directly results in death within 7 days)
2 Minor <ul style="list-style-type: none"> • Clinically overt (including imaging), resulting in hemoglobin drop of 3 to <5 g/dL or $\geq 10\%$ decrease in hematocrit • No observed blood loss: ≥ 4 g/dL decrease in the hemoglobin concentration or $\geq 12\%$ decrease in hematocrit • Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above • Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug) • Leading to or prolonging hospitalization

TIMI Non-Coronary Artery Bypass Graft (CABG) Related Bleeding:
<ul style="list-style-type: none"> Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging)
<p>3. Minimal</p> <p>Any overt bleeding event that does not meet the criteria above</p> <p>Any clinically overt sign of hemorrhage (including imaging) associated with a <3 g/dL decrease in haemoglobin concentration or <9% decrease in hematocrit</p>
Refs 22 , 23

Table 16.3: BARC Bleeding Criteria

BARC
<p>Type 0: No bleeding</p>
<p>Type 1:</p> <p>Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health-care professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a health-care professional.</p>
<p>Type 2:</p> <p>Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria:</p> <ul style="list-style-type: none"> requiring nonsurgical, medical intervention by a health-care professional, leading to hospitalization or increased level of care, or prompting evaluation
<p>Type 3:</p> <p>Type 3a:</p> <p>Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed)</p> <p>Any transfusion with overt bleeding</p> <p>Type 3b:</p> <p>Overt bleeding plus hemoglobin drop ≥ 5 g/dL* (provided hemoglobin drop is related to bleed),</p> <p>Cardiac tamponade,</p>

BARC
<p>Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid),</p> <p>Bleeding requiring intravenous vasoactive agents</p> <p>Type 3c:</p> <p>Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal),</p> <p>Subcategories confirmed by autopsy or imaging or lumbar puncture,</p> <p>Intraocular bleed compromising vision.</p>
<p>Type 4:</p> <p>Coronary artery bypass graft (CABG)-related bleeding,</p> <p>Perioperative intracranial bleeding within 48 h,</p> <p>Reoperation after closure of sternotomy for the purpose of controlling bleeding</p> <p>Transfusion of ≥ 5 U whole blood or packed red blood cells within a 48-h period,</p> <p>Chest tube output more than or equal to 2L within a 24-h period</p>
<p>Type 5:</p> <p>Fatal bleeding</p> <p>Type 5a:</p> <p>Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious</p> <p>Type 5b:</p> <p>Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation</p>
<p>Ref: 18</p>

16.4. Definition of terms

<u>Abnormal liver function</u> is defined as chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., bilirubin >2 times the ULN, in association with aspartate transaminase/alanine transaminase/alkaline phosphatase >3 times the ULN, and so forth).
<u>Abnormal renal function</u> is defined as chronic dialysis, renal transplantation, or serum creatinine $\geq 200 \mu\text{mol/L}$ ($\geq 2.26 \text{ mg/dL}$).
<u>Congestive heart failure</u> is defined as the current presence or prior history of clinical congestive heart requiring medical attention and medical therapy or documented ejection fraction $\leq 35\%$ (left ventricular systolic dysfunction).
<u>Diabetes mellitus</u> includes diabetes requiring treatment with diet only or with pharmacologic therapy (insulin, oral hypoglycemic agents).
<u>Documented clinical need</u> is defined as a known record in any form (incl. written, electronic or verbal) recording pertinent subject data with regard to the clinical reason for the choice of an alternative medication. This reason must be captured and pre-declared before subject randomization.
<u>Labile INRs</u> is defined as unstable or high INRs or poor time in therapeutic range (e.g., <60%) while on a vitamin K antagonist.
<u>Hypertension</u> is defined as hypertension requiring pharmacologic therapy to maintain a BP <140/85 mmHg or untreated hypertension documented by BP >140 mmHg systolic or >90 mmHg diastolic on two separate occasions.
<u>SEE</u> : An abrupt episode of arterial insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of other likely mechanisms (e.g., atherosclerosis, instrumentation)
<p><u>Stroke</u>: A stroke is defined by an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. The event classifies as a stroke rather than a TIA based on any of the following:</p> <ul style="list-style-type: none"> - Duration of neurological dysfunction >24 hrs. - Duration of neurological dysfunction <24 hrs in case of imaging-documented new hemorrhage or infarction. - A neurological dysfunction resulting in death (24)
<u>TIA</u> : TIA is defined by any neurological dysfunction not satisfying the above criteria for stroke, specifically if lasting <24 h without imaging-documented acute brain infarction.

16.5. Components of the CHADS₂, CHA₂DS₂-VASc Score and HAS-BLED Score

Table 16.4: Components of the CHADS₂ Score

CHADS₂-VASc	Score
Congestive heart failure	1
Hypertension (systolic >160 mmHg)	1
Age >75 years	1
Diabetes mellitus	1
Prior cerebral ischemia	2
Maximum score	6

Table 16.5: Components of the CHA₂DS₂-VASc Score

CHA₂DS₂-VASc	Score
Congestive heart failure	1
Hypertension	1
Age ≥75 years	2
Diabetes mellitus	1
Stroke/ transient ischemic attack (TIA)/thrombo-embolism (TE)	2
Vascular disease (prior myocardial infarction [MI], peripheral artery disease [PAD], or aortic plaque)	1
Aged 65 to 74 years	1
Sex category (i.e., female sex)	1
Maximum score	10

Table 16.6: Components of the HAS-BLED Score

HAS-BLED	Score
Hypertension history (systolic blood pressure >160 mmHg systolic)	1
Abnormal renal function (dialysis, transplant, serum creatinine >2.6 mg/dL or >200 µmol/L)	1
Abnormal liver function (cirrhosis or bilirubin >2x ULN [upper limit of normal] with aspartate transaminase [AST]/alanine transaminase [ALT]/alkaline phosphatase [ALP] >3x ULN)	1
Previous history of stroke	1
Prior Major Bleeding or predisposition to bleeding (e.g., anemia)	1
Labile INRs (unstable/high international normalized ratio [INRs], time in therapeutic range [TTR] <60%)	1
Elderly (age >65 years)	1
Drug usage (i.e., antiplatelet agents, non-steroidal anti-inflammatory drugs [NSAIDs])	1
Excessive alcohol use (≥8 drinks/week)	1
Maximum score	9

16.6. Estimation of Creatinine Clearance (CrCL)

Creatinine Clearance Using Cockcroft-Gault Formula (34)

The Cockcroft-Gault formula for the calculation of CrCL will be used in this study.

Creatinine Clearance for Males:

$$\text{CrCL} = [140 - \text{age (years)}] \times [\text{body weight (kg)}] / [72 \times \text{serum creatinine (mg/dL)}]$$

Creatinine Clearance for Females:

$$\text{CrCL} = 0.85 \times [140 - \text{age (years)}] \times [\text{body weight (kg)}] / [72 \times \text{serum creatinine (mg/dL)}]$$

The Chronic Kidney Disease Epidemiology Equation (CKD-EPI) to estimate the glomerular filtration rate (GFR)

The table is taken out of the publication in Annals of Internal medicine 2009 (35).

Table 2. The CKD-EPI Equation for Estimating GFR on the Natural Scale*		
Race and Sex	Serum Creatinine Level, $\mu\text{mol/L}$ (mg/dL)	Equation
Black		
Female	≤ 62 (≤ 0.7)	$\text{GFR} = 166 \times (\text{Scr}/0.7)^{-0.329} \times (0.993)^{\text{Age}}$
	> 62 (> 0.7)	$\text{GFR} = 166 \times (\text{Scr}/0.7)^{-1.209} \times (0.993)^{\text{Age}}$
Male	≤ 80 (≤ 0.9)	$\text{GFR} = 163 \times (\text{Scr}/0.9)^{-0.411} \times (0.993)^{\text{Age}}$
	> 80 (> 0.9)	$\text{GFR} = 163 \times (\text{Scr}/0.9)^{-1.209} \times (0.993)^{\text{Age}}$
White or other		
Female	≤ 62 (≤ 0.7)	$\text{GFR} = 144 \times (\text{Scr}/0.7)^{-0.329} \times (0.993)^{\text{Age}}$
	> 62 (> 0.7)	$\text{GFR} = 144 \times (\text{Scr}/0.7)^{-1.209} \times (0.993)^{\text{Age}}$
Male	≤ 80 (≤ 0.9)	$\text{GFR} = 141 \times (\text{Scr}/0.9)^{-0.411} \times (0.993)^{\text{Age}}$
	> 80 (> 0.9)	$\text{GFR} = 141 \times (\text{Scr}/0.9)^{-1.209} \times (0.993)^{\text{Age}}$

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; GFR = glomerular filtration rate.

* Expressed for specified race, sex, and serum creatinine level. To convert GFR from mL/min per 1.73 m^2 to mL/s per 1.73 m^2 , multiply by 0.0167. We derived equation coefficients from pooled development and internal validation data sets. The CKD-EPI equation, expressed as a single equation, is $\text{GFR} = 141 \times \min(\text{Scr}/\kappa, 1)^\alpha \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ [if female] $\times 1.159$ [if black], where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/ κ or 1, and max indicates the maximum of Scr/ κ or 1. In this table, the multiplication factors for race and sex are incorporated into the intercept, which results in different intercepts for age and sex combinations.

16.7. Modified Rankin Scale

Table 16.7: Modified Rankin Scale

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

16.8. Regional Guideline Recommendations for INR

Table 16.8: Regional Guideline Recommendations for INR

Guideline	Ref.	Target INR Range
Europe and Asia	(15)	2.0 – 3.0
Canada	(36)	2.0 – 3.0

16.9. Schedule of Events

Visit number	0	1	2	3	4	5	6	7	8	9
Period	Screening	Pre-Ablation Treatment		Baseline	Post-Ablation Treatment					Post-Treatment Follow-up
Visit	Screening Visit	Randomization Visit ^a	Optional/ Un-scheduled Visit ^b	CA Visit (Periprocedural Visit)	Hospital Discharge Visit ^c	MRI (if applicable) Visit	Site Visit Day 30	TA or Site Visit Day 60 ^d	EOT Visit ^e	End of Study-Visit ^f
Visit Day		Day -21	Day -14	Day 0 / CA day		Day 4	Day 30	Day 60	Day 90 / EOT	EOT +30 Days
Visit Window days	1-3 days	Max. Day -28	±2	n/a		±2	±5	±7	±7	+5
Inclusion/Exclusion Criteria	X	X								
Demographic Information	X									
Medical History (including bleeding history and cardioversions)	X									
Physical Examination	X									
Study Informed Consent ^g	X									
Randomization by IXRS ^h		X								
Local Lab Results ⁱ	X									
Blood draw for Central Lab ^j	X			X			X		X	
Pregnancy test ^k	X	(X)	(X)	X			X	(X)	(X)	
Blood draw for analysis of cardiac markers	X									
Concomitant Medication (all prior meds in previous 30 days at randomization)	X	X	X	X	X		X	X	X	X
Administer /Dispense assigned Study Medications ^l		X		X						n/a

Visit number	0	1	2	3	4	5	6	7	8	9
Period	Screening	Pre-Ablation Treatment		Baseline	Post-Ablation Treatment					Post-Treatment Follow-up
Visit	Screening Visit	Randomization Visit ^a	Optional/ Un-scheduled Visit ^b	CA Visit (Periprocedural Visit)	Hospital Discharge Visit ^c	MRI (if applicable) Visit	Site Visit Day 30	TA or Site Visit Day 60 ^d	EOT Visit ^e	End of Study-Visit ^f
Visit Day		Day -21	Day -14	Day 0 / CA day		Day 4	Day 30	Day 60	Day 90 / EOT	EOT +30 Days
Visit Window days	1-3 days	Max. Day -28	±2	n/a		±2	±5	±7	±7	+5
Obtain INR and VKA dose information (VKA arm only) ^m		X ⁿ	X	X	X		X	X	X	X
Vital Signs ^o		X	X	X	X	X	X	(X)	X	X
12-lead ECG		X		X	X		X		X	
TEE ^p				X						
Catheter ablation procedure (incl. UFH administration /ACT monitoring)				X						
DW-MRI (selected sites) ^q						X				
Review study regimen compliance & interruptions ^r			X	X			X	X	X	
(S)AE / Events Reporting ^s		X	X	X	X	X	X	X	X	X
Abbreviations: ACT = activated clotting time; AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; ALP = alkaline phosphatase; CA = catheter ablation; CrCL = creatinine clearance; ECG = electrocardiogram; eCRF = electronic case report form; EOT = end- of- treatment; IC = informed consent; INR = international normalized ratio; IXRS = Interactive web/voice response system; (DW-)MRI = (diffusion weighted) magnetic resonance imaging; n/a = not applicable; NOAC = non-vitamin-K antagonist oral anticoagulant; OAC = oral anticoagulant; SAE = serious adverse event; TA = Telephone assessment; TBL = total bilirubin; TEE = trans esophageal echocardiogram; UFH = unfractionated heparin; ULN = upper limit of normal; VKA = vitamin K antagonist.										
^a Visits for Screening and Randomization may be combined if the Inclusion /Exclusion criteria can be checked on the basis of the patient's health record and actual laboratory results with sufficient accuracy and if the patient has been handed out the informed consent form at least one day before randomization and preconditioned that all of the patient's questions could be answered										
^b A personal visit is optional for those patients who do not have the option of INR measurement by their general practitioner.										
^c Hospital Discharge Visit: will be done at the discretion of the Investigator										

^d As an alternative to the TA, a personal visit is optional for those patients who do not have the option of INR measurement by their general practitioner.
^e Subjects are transitioned to an available marketed OAC of the Investigator's choice. The Investigator will follow the transition strategy in the approved product label. Subjects who prematurely discontinue study OAC are requested to continue clinical follow-up with study visits according to this schedule.
^f All randomized subjects who are on study medication (study edoxaban or VKA) at 90 days, will have a mandatory post-treatment contact at 30-35 days after the EOT visit to collect data on concomitant medications, serious AEs, and other safety events of interest.
^g Subjects eligible to participate in the study provide written IC before randomization or any study-specific procedures. Once written IC is obtained, subjects should be randomized without delay.
^h For subjects randomized to edoxaban: If subject is on: (a) VKA, discontinue the VKA, the first dose of edoxaban can be started when INR ≤ 2.5 ; (b) NOAC, discontinue NOAC and start edoxaban at the time of the next scheduled NOAC dose. For subjects randomized to VKA: If subject is on: (a) VKA, continue with medication as provided by IXRS when INR ≤ 2.5 ; (b) NOAC, discontinue the NOAC and start VKA at the time of the next scheduled NOAC dose. See Sections 5.2.1 and 5.2.2 for more detailed information
ⁱ Applicable only when available recent local laboratory results are of sufficient accuracy to verify the patient's eligibility and support randomization in the judgement of the investigator and if Screening and Randomization visits are combined. Check the most recent results from local laboratory tests done: Hemoglobin, platelet count, WBC (with differential if elevated), ALT, AST, total bilirubin (if elevated, determine conjugated/unconjugated bilirubin fraction), Creatinine, and CrCL as estimated by the Cockcroft-Gault formula.
^j Blood draw for central laboratory analysis as described in Sections 6.2 and 9.7. CrCL will be provided as estimated by the Cockcroft-Gault formula. Individual blood samples are collected, stored and shipped according to the Laboratory Manual.
^k Women of childbearing potential must have a negative urine test for pregnancy (obligatory at Visits 0, 3, and 6) and be willing and able to adhere to the prohibitions and restrictions specified in the protocol. Furthermore, pregnancy tests are carried out whenever there are clinical indications for the existence of a pregnancy.
^l Sponsor supplies study subjects with edoxaban and VKA according to assigned regimen at randomization. Medication kits are assigned through the IXRS. Accountability for medications provided is performed at dispensing visits and the EOT visit
^m VKA subjects only: INR values and VKA dose are collected and entered into the eCRF either during the on-site visits or by local laboratory determination. INR values and VKA doses collected through the general practitioner or local anticoagulation clinic must also be considered and collected but this does not constitute a waiver for subjects' planned TA or INR determination during on-site visits. In any case the study physician is responsible for checking the INR value and adapting the VKA dose accordingly.
ⁿ VKA subjects only: Frequent INR determinations upon initiation should be obtained until subject's INR is stable in the therapeutic range. It is expected that more frequent visits will be planned for 'de novo' subjects on VKA to adjust the dose with the goal of reaching INR 2.0-3.0 within 6-8 days after enrolment. Obtain subsequent INR determinations as per recommendations and guidelines provided in the local approved label from the respective VKA manufacturer (see Section 6.2).
^o Vital signs include heart rate, sitting blood pressure, body weight and height. Height only needs to be recorded at randomization.
^p TEE or intracardiac echocardiogram will be performed during the hospital stay related to the procedure directly before catheter ablation or the day before (up to 24 h before ablation).
^q DW-MRI will be performed in a subset of study sites 4 days \pm 2 days post catheter ablation.
^r Antithrombotic regimen compliance is achieved by assessing subject compliance at each visit (both by pill count, self-reporting/ physician-reporting and by INR values for VKA subjects only). In case of a suspected study endpoint, an additional assessment for subject compliance to the assigned regimen must be performed.
^s (S)AEs, endpoint events, and events of special interest should be reported as soon as site personnel learn of the event. Endpoint event and AE reporting should occur throughout the study and not be restricted to specific visits. If ALT or AST $> 3 \times \text{ULN}$ with simultaneous TBL $> 2 \times \text{ULN}$ is observed, then ALP should be determined. Report ongoing all endpoints and all AEs including abnormal laboratory findings. Any laboratory measurements performed during unscheduled visits are collected.